

SUPPLEMENTARY DATA

Supplement to: Tiansheng Wang¹, Jin-liern Hong¹, Emily W Gower¹, Virginia Pate¹, Seema Garg², John B Buse³, Til Stürmer¹. Incretin-based Therapies and Diabetic Retinopathy: Real World Evidence in Older US Adults.

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Supplementary Table 1. Codes used for key covariates in this study.

Diabetes	ICD-9 Codes
Diabetes	250
Eye disease	ICD-9 Codes
Diabetic Retinopathy	362.01-362.07
Blindness and low vision	369
Age-related macular degeneration	362.50, 362.51, 362.52, 362.42, 362.43
Age-related macular degeneration that needs anti-VEGF treatment	362.50, 362.52, 362.42, 362.43
Glaucoma	365
Cataract	366
Retinal detachments and defects	361
Disorders of globe	360
Chorioretinal inflammation	363
disorder of the iris or ciliary body	364
Visual disturbance	368
Keratitis	370
Corneal disorders	371
Disorders of the conjunctiva	372
Inflammation of eyelid	373
Other disorder of eyelid	374
Disorder of lacrimal system	375
Disorder of orbit	376
Optic nerve disorder	377
Strabismus	378
Other disorders of eye	379
Procedures for diabetic retinopathy	CPT Codes
Intravitreal Injection	67028

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Panretinal Photocoagulation	67228
Focal Laser	67210
Vitrectomy	67036, 67038, 67039, 67040, 67041, 67042
Drugs	HCPCS Codes
Triamcinolone	J3300, J3301, J3302, J3303
Dexamethasone	J7312, C9256
Flucinolone	J7313
Ranibizumab	J2778
Aflibercept	J0178, Q2046, C9291
Bevacizumab	J9035, C9257, Q2024
Unclassified/miscellaneous drug codes	J3490, J3590, C9399
Eye Exams/Diagnostic Testing	CPT Codes
Intermediate eye exam, new patient	92002
Intermediate eye exam, established patient	92012
Comprehensive eye exam, new patient	92004
Comprehensive eye exam, established patient	92014
eye exam with anesthesia, complete	92018
eye exam w/ anesthesia, limited	92019
Gonioscopy	92020
Optical coherence tomography	92134
Scanning computerized ophthalmic diagnostic imaging	92135
Ophthalmoscopy, extended w/ retinal drawing, initial	92225
Ophthalmoscopy, extended w/ retinal drawing, subsequent	92226
Fundus angioscopy	92230
Fluorescein angiography	92235
Indocyanine-green angiography	92240
Fundus photography	92250
Ophthalmoscopy/dynamometry	92260

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B-scan ultrasonography	76512
Consult eye codes*	99241-45
Evaluation/Management for established patients involving eye exams*	99213-15
Evaluation/Management for new patients involving eye exams*	99203-05
Health Care Utilization	CPT codes
HbA1c test	83036, 86037, 3044F, 3045F, 3046F
Lipid test	80061, 83704, 3048F, 3049F, 3050F
Office/Outpatient visit, new patient	99201, 99202, 99203, 99204, 99205
Office/Outpatient visit, established patient	99211, 99212, 99213, 99214, 99215
Flu shot	G0008, G9141, G9142, G8108, 90470, 90471, 90660, 90663, 90658,
Emergency room visits	99281, 99282, 99283, 99284, 99295 or PLCSRVC code=23; or revenue center code=0450-0459 or 0981;
Health Care Utilization	ICD 9 codes
Flu shot	V0481, 9952

*We required such codes to be submitted by ophthalmologists or optometrists (physician specialty code 18 or 41).

Reference: Quigley HA, Cassard SD, Gower EW, et al. The **cost of glaucoma care provided to Medicare beneficiaries** from 2002 to 2009. *Ophthalmology*. 2013 Nov;120(11):2249-57. doi: 10.1016/j.ophtha.2013.04.027. Epub 2013 Jun 12.

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Supplementary Table 2. Drugs may induce retinopathy^{1,2}.

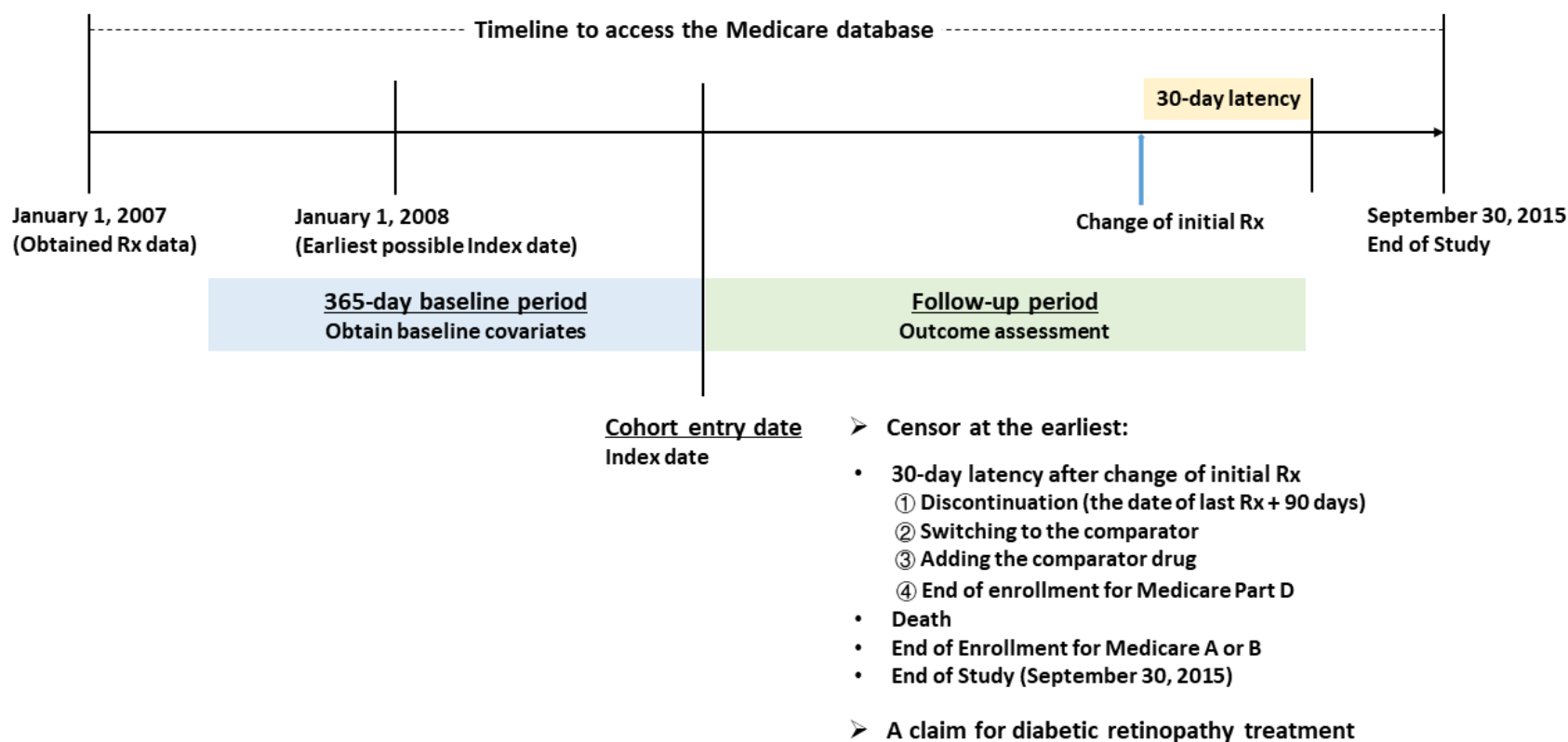
Drug	Adverse Event
Tamoxifen	retinal vein thrombosis; retinopathy
Quinine	blindness
Chloroquine	retinopathy; high dose or long-term use
Hydroxychloroquine	retinal damage with long-term use; retinopathy
Mefloquine	visual disturbance
Digoxin	visual disturbance
Ethambutol	optic neuritis: decrease acuity; blindness, irreversible
Peginterferon Alfa 2a	serious retinal detachment; vision loss or retinopathy, retinal vein thrombosis
Peginterferon Alfa 2b	vision loss or retinopathy, retinal vein thrombosis, retinal detachment
Interferon Alfa-2b	retinal hemorrhage
Interferon alfa n3	visual disturbance
Interferon alfacon 1	vision loss or retinopathy
Interferon Beta 1a	retinal vascular disorder: ie, retinopathy, cotton wool spots or obstruction of retinal artery or vein
Interferon Alfa 1b	retinal hemorrhage
Isocarboxazid	visual disturbance
Sildenafil	retinal hemorrhage, vision loss
Isotretinoin	visual disturbance
Vigabatrin	visual field defect
Fingolimod	macular edema
Docetaxel	macular edema
Niacin	macular edema
Latanoprost (Ophthalmic)	macular edema

Reference

1. Nencini C, Barberi L Fau, Micheli L, et al. Retinopathy induced by drugs and herbal medicines. *Eur Rev Med Pharmacol Sci* 2008; 12: 293-298
2. Makri OE, Georgalas I Fau, Georgakopoulos CD. Drug-induced macular edema. *Drugs* (2013) 73:789–802

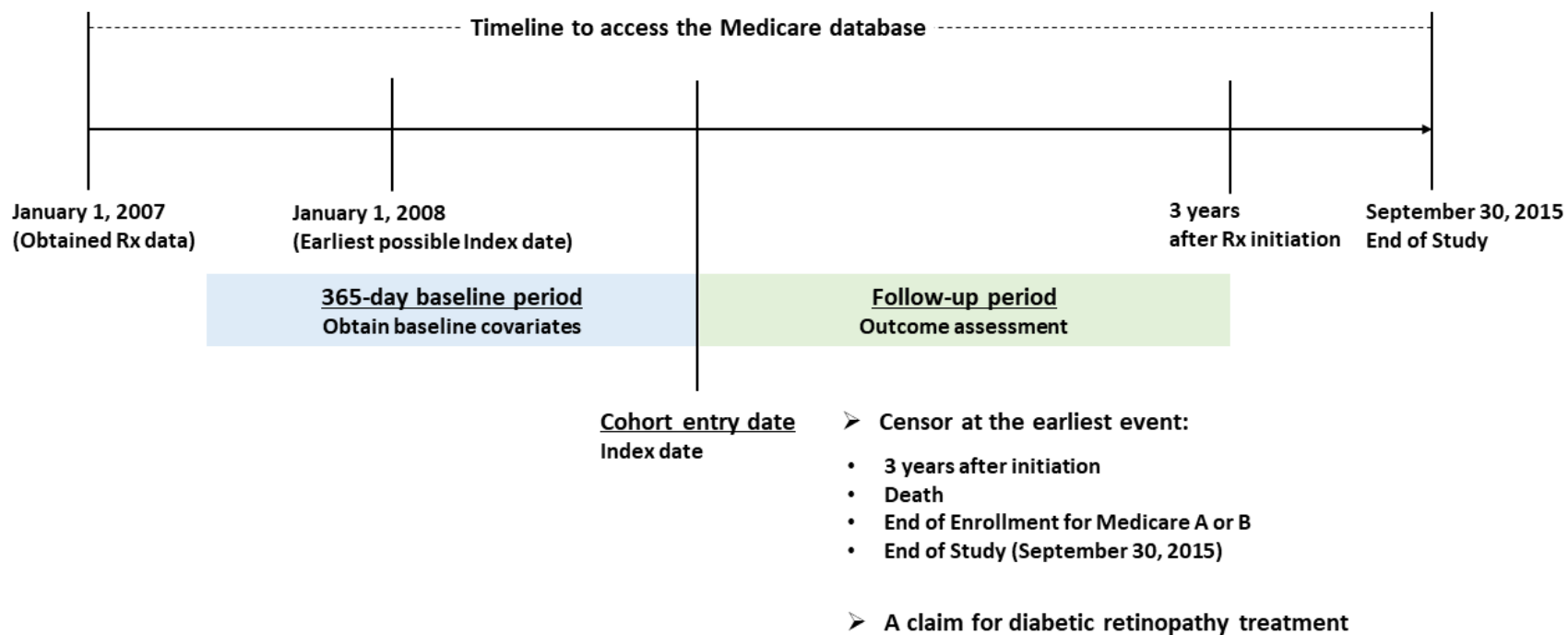
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Supplementary Figure 1. Overview of study design and new user cohort for as treated analysis. Rx, prescription. Treatment discontinuation was defined as no refill within a period equal to the prescribed duration of the last filled prescription (Stopping) plus a grace period of 90 days for incretin-based therapies and their comparators, respectively. Switching is defined as discontinuing the current treatment and started filling the comparator drug. Augmenting is defined as a subsequent addition of a comparator drug. The eligible study population consisted of Medicare enrollees who were at least 65 years old and had at least 12 months of continuous enrolment in Medicare parts A, B and D before initiation. New users were defined as the first dispensing of a prescription in a given drug class after a washout period of 12 months for this drug class.



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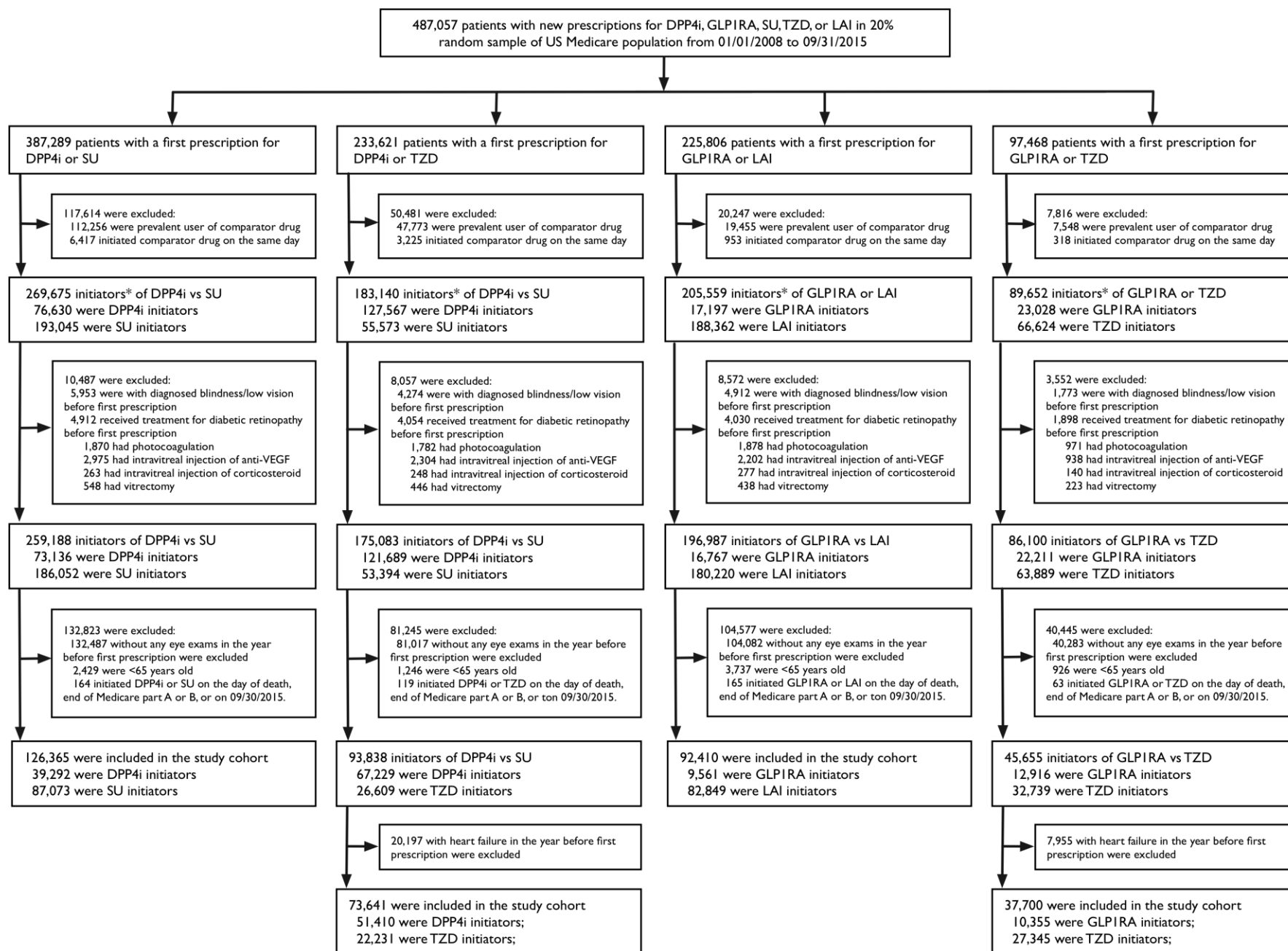
Supplementary Figure 2. Overview of study design and new user cohort for initial treatment analysis. Rx, prescription. The eligible study population consisted of Medicare enrollees who were at least 65 years old and had at least 12 months of continuous enrolment in Medicare parts A, B and D before initiation. New users were defined as the first dispensing of a prescription in a given drug class after a washout period of 12 months for this drug class.



SUPPLEMENTARY DATA

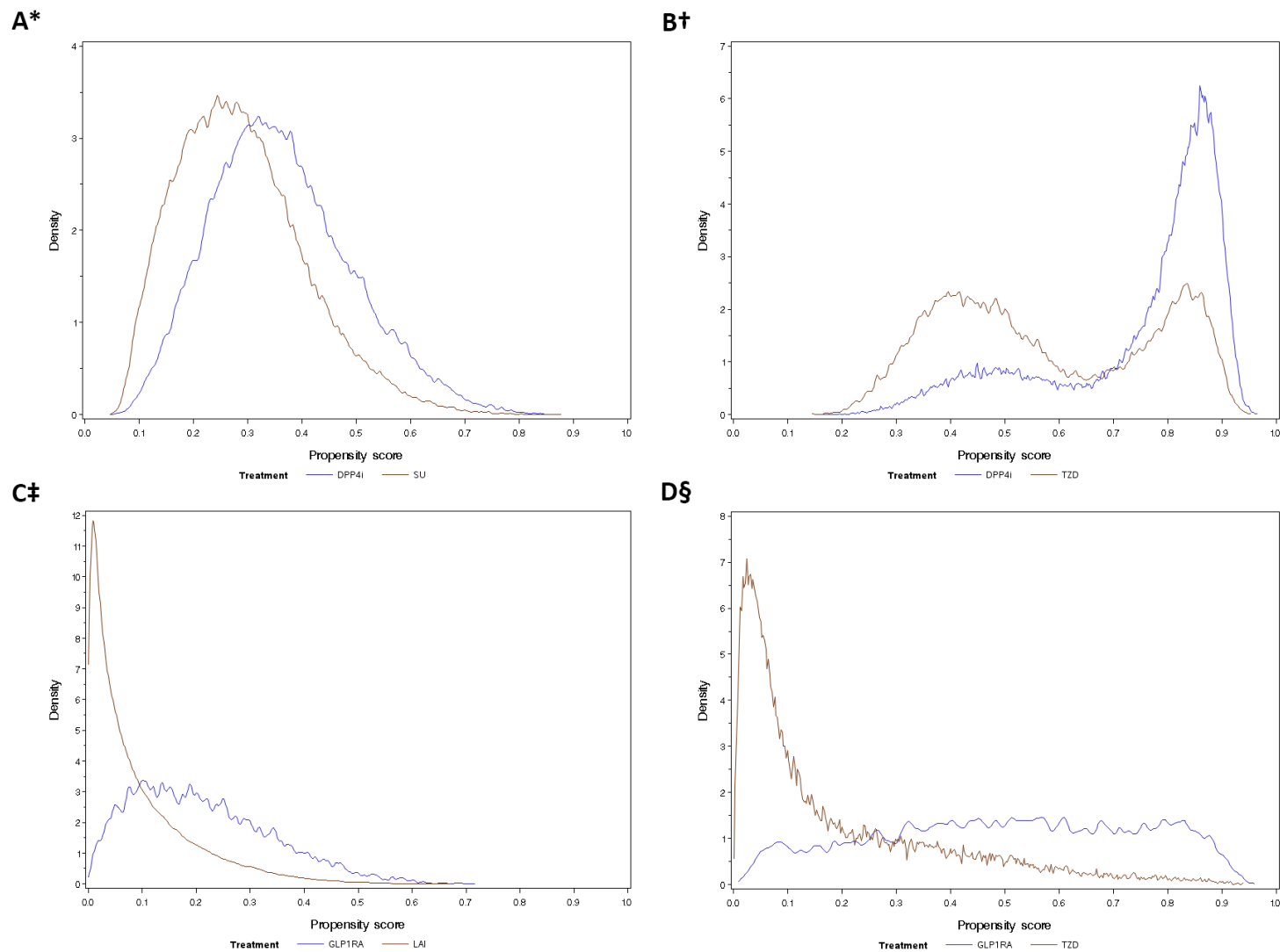
Supplementary Figure 3. Number of Patients in the base cohort and study cohort. DPP4i, DPP-4 inhibitor; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, GLP-1 receptor agonist; LAI, long acting insulin. Initiation defined as having no prescriptions of either drug class during the 12 months prior to initiation. A patient could be a new user of incretin-based therapies or comparator in different periods according to the 12-month washout period definition, thus could be selected in both incretin-based therapies and comparator cohorts in different periods.

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Supplementary Figure 4. Propensity score distribution. DPP4i vs SU cohort (panel A); DPP4i vs TZD cohort (panel B); GLP1RA vs LAI cohort (panel C); GLP1RA vs TZD cohort (panel D). Abbreviations: DPP4i, DPP-4 inhibitor; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP, GLP-1 receptor agonist; LAI, long acting insulin. The “double peak” shape of plot for the propensity score distribution of TZD in DPP4i vs TZD comparison is mainly due to the calendar year dummy variables, i.e. a function of the increased use of DPP4i and decreased use of TZD overtime.



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Supplementary Table 3. Patient characteristics of DPP-4 initiators and comparators*.

Characteristic	DPP4i vs SU					DPP4i vs TZD				
	DPP4i (N†=39,292)	SU (N=87,073)	Unweighted Standardized Difference	Weighted SU (N=39,482)	Weighted Standardized Difference	DPP4i (N†=51,410)	TZD (N=22,231)	Unweighted Standardized Difference	Weighted TZD (N=51,450)	Weighted Standardized Difference
Age, mean (SD)	76.5(7.01)	76.7(7.19)	0.034	76.4(6.99)	0.006	76.0(6.73)	75.4(6.51)	0.086	76.0(6.75)	0.000
Male, n (%)	15,461 (39.3%)	35,631 (40.9%)	0.032	15,504 (39.3%)	0.002	20,307 (39.5%)	9,262 (41.7%)	0.044	20,642 (40.1%)	0.013
Race, n (%)										
White	30,064 (76.5%)	69,824 (80.2%)	0.089	30,268 (76.7%)	0.004	39,951 (77.7%)	16,708 (75.2%)	0.060	40,663 (79.0%)	0.032
Black	4,081 (10.4%)	9,300 (10.7%)	0.010	4,066 (10.3%)	0.003	5,112 (9.9%)	2,301 (10.4%)	0.013	4,698 (9.1%)	0.028
Others	5,147 (13.1%)	7,949 (9.1%)	0.127	5,148 (13.0%)	0.002	6,347 (12.3%)	3,222 (14.5%)	0.063	6,089 (11.8%)	0.016
Calendar year of initiating, n (%)										
2008	2,280 (5.8%)	9,077 (10.4%)	0.170	2,287 (5.8%)	0.000	2,557 (5.0%)	4,004 (18.0%)	0.418	2,561 (5.0%)	0.000
2009	3,065 (7.8%)	12,520 (14.4%)	0.211	3,057 (7.7%)	0.002	3,840 (7.5%)	5,200 (23.4%)	0.452	3,836 (7.5%)	0.000
2010	3,993 (10.2%)	11,933 (13.7%)	0.109	4,008 (10.2%)	0.000	4,925 (9.6%)	4,306 (19.4%)	0.281	4,921 (9.6%)	0.001
2011	6,039 (15.4%)	11,487 (13.2%)	0.062	6,072 (15.4%)	0.000	6,926 (13.5%)	2,454 (11.0%)	0.074	6,959 (13.5%)	0.002
2012	6,316 (16.1%)	10,774 (12.4%)	0.106	6,370 (16.1%)	0.002	7,888 (15.3%)	1,272 (5.7%)	0.317	7,843 (15.2%)	0.003
2013	5,605 (14.3%)	10,989 (12.6%)	0.048	5,623 (14.2%)	0.001	8,162 (15.9%)	1,556 (7.0%)	0.282	8,115 (15.8%)	0.003
2014	6,417 (16.3%)	11,221 (12.9%)	0.098	6,464 (16.4%)	0.001	9,243 (18.0%)	1,776 (8.0%)	0.301	9,307 (18.1%)	0.003

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2015	5,577 (14.2%)	9,072 (10.4%)	0.115	5,601 (14.2%)	0.000	7,869 (15.3%)	1,663 (7.5%)	0.248	7,909 (15.4%)	0.002
Eye comorbidities, n (%)										
Retinopathy	4,555 (11.6%)	8,156 (9.4%)	0.073	4,594 (11.6%)	0.001	6,094 (11.9%)	2,711 (12.2%)	0.010	6,120 (11.9%)	0.001
Age-related macular degeneration	5,173 (13.2%)	11,650 (13.4%)	0.006	5,177 (13.1%)	0.002	6,243 (12.1%)	2,479 (11.2%)	0.031	6,135 (11.9%)	0.007
Retinal detachment and defects	562 (1.4%)	1,271 (1.5%)	0.002	558 (1.4%)	0.001	708 (1.4%)	327 (1.5%)	0.008	710 (1.4%)	0.000
Other retinal disorders	6,671 (17.0%)	13,434 (15.4%)	0.042	6,656 (16.9%)	0.003	8,229 (16.0%)	3,275 (14.7%)	0.035	8,497 (16.5%)	0.014
Cataract	20,852 (53.1%)	47,001 (54.0%)	0.018	20,884 (52.9%)	0.003	27,721 (53.9%)	12,281 (55.2%)	0.027	27,812 (54.1%)	0.003
Glaucoma	11,470 (29.2%)	23,446 (26.9%)	0.050	11,454 (29.0%)	0.004	14,646 (28.5%)	6,031 (27.1%)	0.030	14,467 (28.1%)	0.008
Other eye diseases§	20,202 (51.4%)	42,616 (48.9%)	0.049	20,201 (51.2%)	0.005	25,172 (49.0%)	10,144 (45.6%)	0.067	25,078 (48.7%)	0.004
Diabetes comorbidities, n (%)										
Nephropathy	4,152 (10.6%)	6,981 (8.0%)	0.088	4,231 (10.7%)	0.005	4,920 (9.6%)	1,784 (8.0%)	0.055	4,997 (9.7%)	0.005
Neuropathy	9,359 (23.8%)	16,053 (18.4%)	0.132	9,497 (24.1%)	0.006	11,646 (22.7%)	4,334 (19.5%)	0.077	11,775 (22.9%)	0.006
Cardiovascular comorbidities, n (%)										
Hypertension	36,239 (92.2%)	79,172 (90.9%)	0.047	36,430 (92.3%)	0.002	47,316 (92.0%)	19,959 (89.8%)	0.079	47,251 (91.8%)	0.007
Dyslipidemia	34,813 (88.6%)	72,664 (83.5%)	0.149	35,048 (88.8%)	0.005	45,699 (88.9%)	19,107 (85.9%)	0.089	45,930 (89.3%)	0.012
Coronary	17,011	35,638	0.048	17,106	0.001	17,843 (34.7%)	6,881	0.080	17,777	0.003

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artery disease	(43.3%)	(40.9%)		(43.3%)			(31.0%)		(34.6%)	
Cerebrovascul	9,814	20,423	0.036	9,854	0.000	10,517 (20.5%)	4,066	0.055	10,256	0.013
ar disease	(25.0%)	(23.5%)		(25.0%)			(18.3%)		(19.9%)	
Peripheral	9,258	17,991	0.070	9,259	0.003	9,722 (18.9%)	3,644	0.066	9,535	0.010
vascular	(23.6%)	(20.7%)		(23.5%)			(16.4%)		(18.5%)	
disease										
Congestive	9,067	20,131	0.001	9,127	0.001	NA	NA	NA	NA	NA
Heart Failure	(23.1%)	(23.1%)		(23.1%)						
Other										
comorbidities,										
n (%)										
Chronic	8,264	19,171	0.024	8,271	0.002	7,186 (14.0%)	2,903	0.027	7,053	0.008
obstructive	(21.0%)	(22.0%)		(20.9%)			(13.1%)		(13.7%)	
pulmonary										
disease										
Depression	7,223	14,971	0.031	7,274	0.001	7,511 (14.6%)	2,839	0.054	7,429	0.005
	(18.4%)	(17.2%)		(18.4%)			(12.8%)		(14.4%)	
Cancer	7,918	17,489	0.002	7,908	0.003	9,608 (18.7%)	3,660	0.058	9,723	0.005
	(20.2%)	(20.1%)		(20.0%)			(16.5%)		(18.9%)	
Chronic	11,913	24,822	0.040	11,994	0.001	12,879 (25.1%)	4,640	0.100	12,949	0.003
kidney	(30.3%)	(28.5%)		(30.4%)			(20.9%)		(25.2%)	
disease¶										
Co-										
medications,										
n (%)										
Metformin	25,399	49,479	0.161	25,782	0.014	37,162 (72.3%)	14,924	0.112	37,247	0.002
	(64.6%)	(56.8%)		(65.3%)			(67.1%)		(72.4%)	
SU	NA	87,073	NA	NA	NA	26,736 (52.0%)	12,047	0.044	27,086	0.013
		(100.0%)					(54.2%)		(52.6%)	
TZD	7,384	10,736	0.179	7,586	0.011	NA	22,231	NA	51,450	NA
	(18.8%)	(12.3%)		(19.2%)			(100.0%)		(100.0%)	
DPP4i	39,292	NA	NA	NA	NA	51,410	NA	NA	NA	NA
	(100.0%)					(100.0%)				
GLP1RA	943 (2.4%)	1,480	0.049	991 (2.5%)	0.007	1,219 (2.4%)	623 (2.8%)	0.027	1,249	0.004
		(1.7%)							(2.4%)	
LAI	8,363	12,108	0.195	8,612	0.013	8,187 (15.9%)	3,355	0.023	8,282	0.005
	(21.3%)	(13.9%)		(21.8%)			(15.1%)		(16.1%)	

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Alpha glucodase inhibitor	225 (0.6%)	295 (0.3%)	0.035	234 (0.6%)	0.003	423 (0.8%)	170 (0.8%)	0.007	426 (0.8%)	0.001
Meglitinide	1,819 (4.6%)	2,207 (2.5%)	0.113	1,906 (4.8%)	0.009	1,548 (3.0%)	577 (2.6%)	0.025	1,681 (3.3%)	0.015
ACE inhibitors	17,133 (43.6%)	40,642 (46.7%)	0.062	17,242 (43.7%)	0.001	24,076 (46.8%)	11,020 (49.6%)	0.055	23,940 (46.5%)	0.006
ARBs	13,857 (35.3%)	23,190 (26.6%)	0.188	13,996 (35.4%)	0.004	17,281 (33.6%)	6,293 (28.3%)	0.115	17,227 (33.5%)	0.003
Beta-blockers	21,930 (55.8%)	48,452 (55.6%)	0.003	21,992 (55.7%)	0.002	26,899 (52.3%)	10,351 (46.6%)	0.115	26,867 (52.2%)	0.002
CCBs	15,060 (38.3%)	32,393 (37.2%)	0.023	15,101 (38.2%)	0.002	19,400 (37.7%)	7,758 (34.9%)	0.059	19,149 (37.2%)	0.011
Statins	28,536 (72.6%)	56,987 (65.4%)	0.156	28,741 (72.8%)	0.004	37,329 (72.6%)	15,120 (68.0%)	0.101	37,390 (72.7%)	0.001
Loop diuretics	10,891 (27.7%)	25,207 (28.9%)	0.027	10,939 (27.7%)	0.000	8,865 (17.2%)	3,290 (14.8%)	0.067	9,099 (17.7%)	0.012
Other diuretics	15,861 (40.4%)	34,387 (39.5%)	0.018	15,971 (40.5%)	0.002	20,844 (40.5%)	8,764 (39.4%)	0.023	20,802 (40.4%)	0.002
Fenofibrate	3,312 (8.4%)	5,641 (6.5%)	0.074	3,388 (8.6%)	0.005	4,498 (8.7%)	1,675 (7.5%)	0.044	4,585 (8.9%)	0.006
Any drugs may induce retinopathy or macular edema**	7,983 (20.3%)	17,846 (20.5%)	0.004	8,030 (20.3%)	0.001	8,762 (17.0%)	3,600 (16.2%)	0.023	9,090 (17.7%)	0.016
Health care utilizations, n (%)										
No. of hyperglycemia diagnosis										
0	20,302 (51.7%)	51,432 (59.1%)	0.149	20,248 (51.3%)	0.008	25,128 (48.9%)	11,653 (52.4%)	0.071	25,234 (49.0%)	0.003
1	5,249 (13.4%)	11,714 (13.5%)	0.003	5,271 (13.4%)	0.000	7,029 (13.7%)	2,902 (13.1%)	0.018	7,035 (13.7%)	0.000
2	3,106	6,149	0.032	3,133	0.001	4,231 (8.2%)	1,711	0.020	4,157	0.006

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	(7.9%)	(7.1%)		(7.9%)		(7.7%)		(8.1%)		
≥3	10,635 (27.1%)	17,778 (20.4%)	0.157	10,830 (27.4%)	0.008	15,022 (29.2%)	5,965 (26.8%)	0.053	15,025 (29.2%)	0.000
No. of hospitalizations due to diabetes										
0	38,627 (98.3%)	85,759 (98.5%)	0.015	38,810 (98.3%)	0.001	50,730 (98.7%)	21,991 (98.9%)	0.022	50,850 (98.8%)	0.014
1	592 (1.5%)	1,177 (1.4%)	0.013	595 (1.5%)	0.000	613 (1.2%)	221 (1.0%)	0.019	530 (1.0%)	0.015
≥2	73 (0.2%)	137 (0.2%)	0.007	77 (0.2%)	0.002	67 (0.1%)	19 (0.1%)	0.014	71 (0.1%)	0.002
No. of ED visit due to diabetes										
0	37,929 (96.5%)	84,164 (96.7%)	0.007	38,104 (96.5%)	0.001	49,715 (96.7%)	21,506 (96.7%)	0.002	49,804 (96.8%)	0.006
1	1,072 (2.7%)	2,417 (2.8%)	0.003	1,084 (2.7%)	0.001	1,388 (2.7%)	610 (2.7%)	0.003	1,351 (2.6%)	0.005
≥2	291 (0.7%)	492 (0.6%)	0.022	293 (0.7%)	0.000	307 (0.6%)	115 (0.5%)	0.011	295 (0.6%)	0.003
Physician encounters										
0	863 (2.2%)	2,813 (3.2%)	0.064	853 (2.2%)	0.002	935 (1.8%)	553 (2.5%)	0.046	853 (1.7%)	0.012
1-3	3,105 (7.9%)	9,546 (11.0%)	0.105	3,083 (7.8%)	0.003	4,088 (8.0%)	2,381 (10.7%)	0.095	4,030 (7.8%)	0.004
4-6	6,103 (15.5%)	15,914 (18.3%)	0.073	6,124 (15.5%)	0.001	9,183 (17.9%)	4,614 (20.8%)	0.073	9,197 (17.9%)	0.000
≥7	29,221 (74.4%)	58,800 (67.5%)	0.151	29,421 (74.5%)	0.003	37,204 (72.4%)	14,683 (66.0%)	0.137	37,370 (72.6%)	0.006
ED visit (any reason)										
0	23,382 (59.5%)	49,093 (56.4%)	0.063	23,475 (59.5%)	0.001	34,385 (66.9%)	15,311 (68.9%)	0.043	34,616 (67.3%)	0.008
1	7,396 (18.8%)	17,173 (19.7%)	0.023	7,454 (18.9%)	0.001	9,376 (18.2%)	3,908 (17.6%)	0.017	9,308 (18.1%)	0.004

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≥ 2	8,514 (21.7%)	20,807 (23.9%)	0.053	8,553 (21.7%)	0.000	7,649 (14.9%)	3,012 (13.5%)	0.038	7,526 (14.6%)	0.007
Flu vaccine	24,181 (61.5%)	51,775 (59.5%)	0.043	24,306 (61.6%)	0.000	31,935 (62.1%)	12,989 (58.4%)	0.075	32,402 (63.0%)	0.018
Low income subsidy	16,130 (41.1%)	31,169 (35.8%)	0.108	16,117 (40.8%)	0.005	18,562 (36.1%)	8,598 (38.7%)	0.053	17,360 (33.7%)	0.050
Lab results#										
HbA1c††										
<7% (53mmol/mol)	17,155(43.6 %)	38,589(44. 3%)	0.019	17,175(43. 5%)	0.003	17,024(33.1%)	7,863(35.4 %)	0.048	16,976(33. 0%)	0.004
7-9% (53-75 mmol/mol)	15,078(38.4 %)	32,919(37. 8%)	0.019	15,186(38. 5%)	0.002	24,629(47.9%)	10,080(45. 3%)	0.052	24,811(48. 2%)	0.007
>9% (75mmol/mol)	7,059(18.0%)	15,565(17. 9%)	0.012	7,124(18.1 %)	0.002	9,758(19.0%)	4,288(19.3 %)	0.022	9,691(18.8 %)	0.006
SBP††										
<130 mmHg	15,654(39.8 %)	31,962(36. 7%)	0.065	15,730(39. 8%)	0.001	20,011(38.9%)	7,332(33.0 %)	0.124	20,238(39. 3%)	0.009
130-139 mmHg	11,065(28.2 %)	25,159(28. 9%)	0.020	11,124(28. 2%)	0.001	14,289(27.8%)	6,746(30.3 %)	0.058	14,258(27. 7%)	0.005
≥ 140 mmHg	12,573(32.0 %)	29,952(34. 4%)	0.057	12,631(32. 0%)	0.001	17,110(33.3%)	8,153(36.7 %)	0.073	16,981(33. 0%)	0.006
DBP††										
<80 mmHg	24,971(63.5 %)	55,020(63. 2%)	0.021	25,100(63. 6%)	0.001	31,118(60.5%)	13,521(60. 8%)	0.027	31,251(60. 7%)	0.005
80-89 mmHg	11,312(28.8 %)	26,097(30. 0%)	0.031	11,366(28. 8%)	0.001	15,912(30.9%)	6,752(30.4 %)	0.025	15,914(30. 9%)	0.004
≥ 90 mmHg	3,010(7.7%)	5,956(6.8%)	0.036	3,019(7.7%)	0.002	4,381(8.5%)	1,958(8.8%)	0.026	4,312(8.4%)	0.007
LDL-C††										
<100 mg/dl	29,116(74.1 %)	63,202(72. 6%)	0.036	29,262(74. 1%)	0.001	37,028(72.0%)	15,740(70. 8%)	0.028	37,216(72. 3%)	0.007
100-129 mg/dl	6,539(16.6%)	14,478(16. 6%)	0.020	6,575(16.7 %)	0.001	8,842(17.2%)	4,000(18.0 %)	0.028	8,824(17.1 %)	0.006
≥ 130 mg/dl	3,638(9.3%)	9,394(10.8 %)	0.051	3,648(9.2%)	0.001	5,540(10.8%)	2,491(11.2 %)	0.030	5,437(10.6 %)	0.007

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Abbreviations: No, number; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin; ACE inhibitors, Angiotension-converting enzyme inhibitors; ARB, angiotension receptor blockers; CCBs, calcium-channel blockers; ED, emergency department; NA, not applicable. HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement.

*The comparisons were defined by use of IBT and PS-weighted comparator. Covariates were measured in 12 months before cohort entry including the index date (New users appear to 100% have the treatment at baseline). Initiation defined as having no prescriptions of either drug class during the 12 months prior to initiation.

† The size of the population for a specific drug differed across cohorts because of the requirement not to have been treated prior to index date with the comparator drug class (Figure S1).

‡ Weighted by standardizing to their distribution in incretin-based therapy initiators by using weights of one for incretin-based therapy initiators and the odds of the estimated propensity score for comparator initiators.

§ Other eye disease included disorders of globe (ICD-9-CM 360), chorioretinal inflammation (ICD-9-CM 363), disorder of the iris or ciliary body (ICD-9-CM 364), visual disturbance (ICD-9-CM 368), keratitis (ICD-9-CM 370), corneal disorders (ICD-9-CM 371), disorders of the conjunctiva (ICD-9-CM 372), inflammation of eyelid (ICD-9-CM 373), other disorder of eyelid (ICD-9-CM 374), disorder of lacrimal system (ICD-9-CM 375), disorder of orbit (ICD-9-CM 376), optic nerve disorder (ICD-9-CM 377), strabismus (ICD-9-CM 378), and other disorders of eye (ICD-9-CM 379).

|| Patients with congestive baseline heart failure were excluded for GLP1RA vs TZD and DPP4i vs TZD comparison; and patients are required not to have been treated prior to index date with the comparator drug class.

¶ Diabetic nephropathy codes (250.40-250.43) were not included to identify chronic kidney disease (ICD-9-CM codes: 016.0; 095.4; 189.0; 189.9; 223.0; 236.91; 271.4; 274.1; 283.11; 403; 404; 440.1; 442.1; 572.4; 581-588; 591; 753.12-753.19; 753.2; 794.4).

** Drugs may induce diabetic retinopathy or macular edema included tamoxifen, quinine, chloroquine, hydroxychloroquine, mefloquine, digoxin, ethambutol, peginterferonalfa 2a, peginterferonalfa 2b, interferon alfa-2b, interferon alfa n3, interferon alfacon 1, interferon beta 1a, interferon alfa 1b, isocarboxazid, sildenafil, isotretinoin, vigabatrin, fingolimod, doxetaxel, niacin, and latanoprost (ophthalmic).

#Based on the measure closest to index date.

†† For clinical measures, the distribution of covariates and standardized difference were the mean of results from multiple imputation (20 iterations) as each iteration produces different number of patients with each level of clinical measure, e.g. HbA1c <7% (53mmol/mol), 7-9% (53-75mmol/mol), >9% (75mmol/mol). Availability and distribution of clinical measures were shown in Table 1.

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Supplementary Table 4. Patient characteristics of GLP-1 receptor agonist initiators and comparators*.

Characteristic	GLP1RA vs LAI					GLP1RA vs TZD				
	GLP1RA (N†=9,561)	LAI (N=82,849)	Unweighted Standardized Difference	Weighted LAI (N=9,595)	Weighted Standardized Difference	GLP1RA (N†=10,355)	TZD (N=27,345)	Unweighted Standardized Difference	Weighted TZD (N=10,768)	Weighted Standardize d Difference
Age, mean (SD)	73.0(5.17)	76.9(7.49)	0.609	73.0(5.18)	0.003	72.7(5.01)	75.5(6.51)	0.480	72.5(5.01)	0.035
Male, n (%)	3,970 (41.5%)	35,069 (42.3%)	0.016	3,986 (41.5%)	0.000	4,018 (38.8%)	11,424 (41.8%)	0.061	4,242 (39.4%)	0.012
Race, n (%)										
White	8,279 (86.6%)	64,568 (77.9%)	0.228	8,304 (86.5%)	0.001	8,809 (85.1%)	20,234 (74.0%)	0.277	9,294 (86.3%)	0.035
Black	599 (6.3%)	10,434 (12.6%)	0.218	606 (6.3%)	0.002	795 (7.7%)	2,819 (10.3%)	0.092	747 (6.9%)	0.028
Others	683 (7.1%)	7,847 (9.5%)	0.084	685 (7.1%)	0.000	751 (7.3%)	4,292 (15.7%)	0.267	727 (6.7%)	0.020
Calendar year of initiating, n (%)										
2008	527 (5.5%)	7,583 (9.2%)	0.140	524 (5.5%)	0.002	288 (2.8%)	4,280 (15.7%)	0.456	285 (2.6%)	0.008
2009	590 (6.2%)	10,474 (12.6%)	0.223	587 (6.1%)	0.002	433 (4.2%)	5,860 (21.4%)	0.534	429 (4.0%)	0.010
2010	775 (8.1%)	10,400 (12.6%)	0.147	773 (8.1%)	0.002	557 (5.4%)	5,094 (18.6%)	0.416	551 (5.1%)	0.012
2011	1,108 (11.6%)	10,762 (13.0%)	0.043	1,100 (11.5%)	0.004	923 (8.9%)	3,113 (11.4%)	0.082	914 (8.5%)	0.015
2012	1,361 (14.2%)	11,361 (13.7%)	0.015	1,364 (14.2%)	0.001	1,410 (13.6%)	1,691 (6.2%)	0.251	1,383 (12.8%)	0.023
2013	1,674 (17.5%)	11,471 (13.8%)	0.101	1,701 (17.7%)	0.006	1,984 (19.2%)	2,164 (7.9%)	0.333	2,105 (19.6%)	0.010
2014	1,713 (17.9%)	11,373 (13.7%)	0.115	1,719 (17.9%)	0.000	2,296 (22.2%)	2,686 (9.8%)	0.342	2,451 (22.8%)	0.014
2015	1,813	9,425	0.213	1,827	0.002	2,464 (23.8%)	2,457	0.408	2,650	0.019

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	(19.0%)	(11.4%)		(19.0%)		(9.0%)		(24.6%)		
Eye comorbidities, n (%)										
Retinopathy	1,025 (10.7%)	11,734 (14.2%)	0.104	1,032 (10.8%)	0.001	1,382 (13.3%)	3,447 (12.6%)	0.022	1,402 (13.0%)	0.010
Age-related macular degeneration	885 (9.3%)	10,975 (13.2%)	0.127	886 (9.2%)	0.001	951 (9.2%)	3,074 (11.2%)	0.068	935 (8.7%)	0.018
Retinal detachment and defects	153 (1.6%)	1,168 (1.4%)	0.016	151 (1.6%)	0.002	176 (1.7%)	399 (1.5%)	0.019	178 (1.7%)	0.003
Other retinal disorders	1,561 (16.3%)	13,871 (16.7%)	0.011	1,568 (16.3%)	0.000	1,702 (16.4%)	4,098 (15.0%)	0.040	1,796 (16.7%)	0.007
Cataract	5,439 (56.9%)	42,068 (50.8%)	0.123	5,457 (56.9%)	0.000	5,817 (56.2%)	14,983 (54.8%)	0.028	6,095 (56.6%)	0.009
Glaucoma	2,374 (24.8%)	22,038 (26.6%)	0.041	2,402 (25.0%)	0.005	2,554 (24.7%)	7,619 (27.9%)	0.073	2,662 (24.7%)	0.001
Other eye diseases§	4,514 (47.2%)	39,448 (47.6%)	0.008	4,536 (47.3%)	0.001	4,863 (47.0%)	12,722 (46.5%)	0.009	5,067 (47.1%)	0.002
Diabetes comorbidities, n (%)										
Nephropathy	1,031 (10.8%)	13,331 (16.1%)	0.156	1,030 (10.7%)	0.001	1,332 (12.9%)	2,382 (8.7%)	0.134	1,367 (12.7%)	0.005
Neuropathy	2,497 (26.1%)	23,903 (28.9%)	0.061	2,515 (26.2%)	0.002	3,106 (30.0%)	5,622 (20.6%)	0.218	3,332 (30.9%)	0.021
Cardiovascular comorbidities, n (%)										
Hypertension	8,797 (92.0%)	77,018 (93.0%)	0.036	8,833 (92.1%)	0.002	9,589 (92.6%)	24,663 (90.2%)	0.086	10,018 (93.0%)	0.017
Dyslipidemia	8,742 (91.4%)	69,448 (83.8%)	0.233	8,785 (91.6%)	0.005	9,436 (91.1%)	23,736 (86.8%)	0.138	9,852 (91.5%)	0.013
Coronary artery disease	3,560 (37.2%)	41,977 (50.7%)	0.273	3,569 (37.2%)	0.001	3,596 (34.7%)	8,592 (31.4%)	0.070	3,681 (34.2%)	0.011

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Cerebrovascular disease	1,629 (17.0%)	25,924 (31.3%)	0.338	1,622 (16.9%)	0.003	1,728 (16.7%)	4,991 (18.3%)	0.041	1,811 (16.8%)	0.004
Peripheral vascular disease	1,632 (17.1%)	23,533 (28.4%)	0.273	1,633 (17.0%)	0.001	1,689 (16.3%)	4,630 (16.9%)	0.017	1,732 (16.1%)	0.006
Congestive Heart Failure	1,501 (15.7%)	28,941 (34.9%)	0.454	1,494 (15.6%)	0.003	NA	NA	NA	NA	NA
Other comorbidities, n (%)										
Chronic obstructive pulmonary disease	1,543 (16.1%)	23,423 (28.3%)	0.295	1,550 (16.2%)	0.000	1,408 (13.6%)	3,539 (12.9%)	0.019	1,464 (13.6%)	0.000
Depression	1,570 (16.4%)	19,073 (23.0%)	0.166	1,568 (16.3%)	0.002	1,838 (17.7%)	3,443 (12.6%)	0.144	1,944 (18.1%)	0.008
Cancer	1,636 (17.1%)	18,537 (22.4%)	0.133	1,632 (17.0%)	0.003	1,767 (17.1%)	4,544 (16.6%)	0.012	1,814 (16.8%)	0.006
Chronic kidney disease¶	2,327 (24.3%)	36,390 (43.9%)	0.422	2,340 (24.4%)	0.001	2,593 (25.0%)	6,032 (22.1%)	0.070	2,709 (25.2%)	0.003
Co-medications, n (%)										
Metformin	6,969 (72.9%)	44,333 (53.5%)	0.410	7,016 (73.1%)	0.005	7,038 (68.0%)	18,736 (68.5%)	0.012	7,303 (67.8%)	0.003
SU	5,695 (59.6%)	49,977 (60.3%)	0.015	5,831 (60.8%)	0.025	5,036 (48.6%)	15,461 (56.5%)	0.159	5,195 (48.2%)	0.008
TZD	2,180 (22.8%)	14,537 (17.5%)	0.131	2,237 (23.3%)	0.012	NA	27,345 (100.0%)	NA	NA	NA
DPP4i	3,594 (37.6%)	20,581 (24.8%)	0.278	3,716 (38.7%)	0.024	3,301 (31.9%)	5,532 (20.2%)	0.268	3,660 (34.0%)	0.045
GLP1RA	9,561 (100.0%)	NA	NA	NA	NA	10,355 (100.0%)	NA	NA	NA	NA
LAI	NA	82,849 (100.0%)	NA	NA	NA	4,229 (40.8%)	4,006 (14.6%)	0.612	4,657 (43.2%)	0.049
Alpha	148 (1.5%)	979 (1.2%)	0.032	154 (1.6%)	0.005	132 (1.3%)	269 (1.0%)	0.028	188 (1.7%)	0.039

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glucodase inhibitor										
Meglitinide	374 (3.9%)	3,846 (4.6%)	0.036	393 (4.1%)	0.009	326 (3.1%)	869 (3.2%)	0.002	333 (3.1%)	0.003
ACE inhibitors	4,401 (46.0%)	40,539 (48.9%)	0.058	4,419 (46.1%)	0.001	4,849 (46.8%)	13,504 (49.4%)	0.051	4,996 (46.4%)	0.009
ARBs	3,532 (36.9%)	22,644 (27.3%)	0.207	3,576 (37.3%)	0.007	3,838 (37.1%)	8,196 (30.0%)	0.151	4,070 (37.8%)	0.015
Beta-blockers	5,002 (52.3%)	49,548 (59.8%)	0.151	5,032 (52.4%)	0.003	5,325 (51.4%)	12,904 (47.2%)	0.085	5,596 (52.0%)	0.011
CCBs	3,289 (34.4%)	33,556 (40.5%)	0.126	3,318 (34.6%)	0.004	3,634 (35.1%)	9,706 (35.5%)	0.008	3,724 (34.6%)	0.011
Statins	7,230 (75.6%)	56,132 (67.8%)	0.175	7,254 (75.6%)	0.000	7,882 (76.1%)	19,024 (69.6%)	0.148	8,134 (75.5%)	0.013
Loop diuretics	2,403 (25.1%)	33,119 (40.0%)	0.321	2,415 (25.2%)	0.001	2,164 (20.9%)	3,979 (14.6%)	0.167	2,350 (21.8%)	0.023
Other diuretics	4,172 (43.6%)	30,603 (36.9%)	0.137	4,201 (43.8%)	0.003	4,414 (42.6%)	10,821 (39.6%)	0.062	4,643 (43.1%)	0.010
Fenofibrate	1,035 (10.8%)	5,797 (7.0%)	0.135	1,062 (11.1%)	0.008	1,138 (11.0%)	2,170 (7.9%)	0.104	1,195 (11.1%)	0.003
Any drugs may induce retinopathy or macular edema**	1,741 (18.2%)	18,794 (22.7%)	0.111	1,758 (18.3%)	0.003	1,685 (16.3%)	4,448 (16.3%)	0.000	1,866 (17.3%)	0.028
Health care utilizations, n (%)										
No. of hyperglycemia diagnosis										
0	4,270 (44.7%)	31,322 (37.8%)	0.140	4,258 (44.4%)	0.006	3,947 (38.1%)	13,788 (50.4%)	0.250	3,958 (36.8%)	0.028
1	1,312 (13.7%)	12,410 (15.0%)	0.036	1,311 (13.7%)	0.002	1,283 (12.4%)	3,548 (13.0%)	0.018	1,330 (12.4%)	0.001
2	833 (8.7%)	7,993 (9.6%)	0.032	843 (8.8%)	0.003	898 (8.7%)	2,163 (7.9%)	0.028	889 (8.3%)	0.015

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≥ 3	3,146 (32.9%)	31,124 (37.6%)	0.098	3,182 (33.2%)	0.006	4,227 (40.8%)	7,846 (28.7%)	0.257	4,591 (42.6%)	0.037
No. of hospitalizations due to diabetes										
0	9,521 (99.6%)	78,850 (95.2%)	0.279	9,554 (99.6%)	0.001	10,270 (99.2%)	27,037 (98.9%)	0.031	10,692 (99.3%)	0.014
1	39 (0.4%)	3,660 (4.4%)	0.264	40 (0.4%)	0.001	76 (0.7%)	282 (1.0%)	0.032	71 (0.7%)	0.009
≥ 2	NTSR	339 (0.4%)	0.087	NTSR	0.000	NTSR	26 (0.1%)	0.003	NTSR	0.018
No. of ED visit due to diabetes										
0	9,393 (98.2%)	75,432 (91.0%)	0.324	9,426 (98.2%)	0.000	10,071 (97.3%)	26,434 (96.7%)	0.034	10,467 (97.2%)	0.003
1	151 (1.6%)	6,111 (7.4%)	0.283	152 (1.6%)	0.000	245 (2.4%)	756 (2.8%)	0.025	253 (2.4%)	0.001
≥ 2	17 (0.2%)	1,306 (1.6%)	0.150	17 (0.2%)	0.000	39 (0.4%)	155 (0.6%)	0.028	48 (0.4%)	0.010
Physician encounters										
0	76 (0.8%)	4,173 (5.0%)	0.254	75 (0.8%)	0.001	95 (0.9%)	612 (2.2%)	0.106	103 (1.0%)	0.004
1-3	567 (5.9%)	8,828 (10.7%)	0.172	554 (5.8%)	0.007	564 (5.4%)	2,750 (10.1%)	0.173	583 (5.4%)	0.002
4-6	1,499 (15.7%)	12,005 (14.5%)	0.033	1,479 (15.4%)	0.007	1,585 (15.3%)	5,502 (20.1%)	0.126	1,559 (14.5%)	0.023
≥ 7	7,419 (77.6%)	57,843 (69.8%)	0.177	7,486 (78.0%)	0.010	8,111 (78.3%)	18,481 (67.6%)	0.244	8,523 (79.2%)	0.020
ED visit (any reason)										
0	6,808 (71.2%)	35,073 (42.3%)	0.609	6,859 (71.5%)	0.006	7,348 (71.0%)	18,947 (69.3%)	0.037	7,581 (70.4%)	0.012
1	1,561 (16.3%)	17,823 (21.5%)	0.133	1,554 (16.2%)	0.003	1,768 (17.1%)	4,728 (17.3%)	0.006	1,918 (17.8%)	0.019
≥ 2	1,192	29,953	0.575	1,181	0.005	1,239 (12.0%)	3,670	0.044	1,269	0.006

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	(12.5%)	(36.2%)		(12.3%)		(13.4%)		(11.8%)		
Flu vaccine	6,193 (64.8%)	47,641 (57.5%)	0.150	6,217 (64.8%)	0.001	6,683 (64.5%)	16,084 (58.8%)	0.118	7,014 (65.1%)	0.013
Low income subsidy	2,572 (26.9%)	36,133 (43.6%)	0.355	2,578 (26.9%)	0.001	2,803 (27.1%)	10,864 (39.7%)	0.271	2,792 (25.9%)	0.026
Lab results#										
HbA1c††										
<7%	3,080 (32.2%)	23,885 (28.8%)	0.073	3,051 (31.8%)	0.009	2,741 (26.5%)	9,316 (34.1%)	0.166	2,803 (26.0%)	0.010
(53mmol/mol)										
7-9% (53-75 mmol/mol)	4,601 (48.1%)	35,146 (42.4%)	0.115	4,647 (48.5%)	0.007	5,029 (48.6%)	12,890 (47.1%)	0.037	5,221 (48.5%)	0.005
>9%	1,879 (19.7%)	23,817 (28.7%)	0.214	1,891 (19.7%)	0.002	2,585 (25.0%)	5,138 (18.8%)	0.150	2,740 (25.5%)	0.013
(75mmol/mol)										
SBP††										
<130 mmHg	3,591 (37.6%)	31,795 (38.4%)	0.042	3,600 (37.5%)	0.001	4,036 (39.0%)	9,233 (33.8%)	0.111	4,234 (39.3%)	0.009
130-139 mmHg	3,232 (33.8%)	23,570 (28.5%)	0.116	3,238 (33.8%)	0.002	3,310 (32.0%)	8,427 (30.8%)	0.040	3,388 (31.5%)	0.012
>=140 mmHg	2,738 (28.7%)	27,484 (33.2%)	0.099	2,751 (28.7%)	0.002	3,009 (29.1%)	9,686 (35.4%)	0.137	3,141 (29.2%)	0.008
DBP††										
<80 mmHg	5,680 (59.4%)	52,952 (63.9%)	0.093	5,688 (59.3%)	0.002	6,209 (60.0%)	15,905 (58.2%)	0.053	6,434 (59.8%)	0.009
80-89 mmHg	3,310 (34.6%)	23,503 (28.4%)	0.135	3,326 (34.7%)	0.002	3,419 (33.0%)	8,469 (31.0%)	0.052	3,581 (33.3%)	0.009
>=90 mmHg	572 (6.0%)	6,395 (7.7%)	0.074	575 (6.0%)	0.002	727 (7.0%)	2,971 (10.9%)	0.136	749 (7.0%)	0.006
LDL-C††										
<100 mg/dl	7,220 (75.5%)	62,906 (75.9%)	0.027	7,238 (75.5%)	0.002	7,717 (74.5%)	18,975 (69.4%)	0.115	8,076 (75.0%)	0.013
100-129 mg/dl	1,512 (15.8%)	12,253 (14.8%)	0.032	1,518 (15.8%)	0.003	1,647 (15.9%)	5,021 (18.4%)	0.065	1,692 (15.7%)	0.008
≥130 mg/dl	829 (8.7%)	7,690 (9.3%)	0.031	832 (8.7%)	0.001	990 (9.6%)	3,348 (12.2%)	0.087	995 (9.2%)	0.012

Abbreviations: No, number; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin; ACE inhibitors, Angiotension-converting enzyme inhibitors; ARB, angiotension receptor blockers; CCBs,

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calcium-channel blockers; ED, emergency department; NA, not applicable. HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement.

*The comparisons were defined by use of IBT and PS-weighted comparator. Covariates were measured in 12 months before cohort entry including the index date (New users appear to 100% have the treatment at baseline). Initiation defined as having no prescriptions of either drug class during the 12 months prior to initiation.

† The size of the population for a specific drug differed across cohorts because of the requirement not to have been treated prior to index date with the comparator drug class (Figure S1).

‡ Weighted by standardizing to their distribution in incretin-based therapy initiators by using weights of one for incretin-based therapy initiators and the odds of the estimated propensity score for comparator initiators.

§ Other eye disease included disorders of globe (ICD-9-CM 360), chorioretinal inflammation (ICD-9-CM 363), disorder of the iris or ciliary body (ICD-9-CM 364), visual disturbance (ICD-9-CM 368), keratitis (ICD-9-CM 370), corneal disorders (ICD-9-CM 371), disorders of the conjunctiva (ICD-9-CM 372), inflammation of eyelid (ICD-9-CM 373), other disorder of eyelid (ICD-9-CM 374), disorder of lacrimal system (ICD-9-CM 375), disorder of orbit (ICD-9-CM 376), optic nerve disorder (ICD-9-CM 377), strabismus (ICD-9-CM 378), and other disorders of eye (ICD-9-CM 379).

|| Patients with congestive baseline heart failure were excluded for GLP1RA vs TZD and DPP4i vs TZD comparison; and patients are required not to have been treated prior to index date with the comparator drug class.

¶ Diabetic nephropathy codes (250.40-250.43) were not included to identify chronic kidney disease (ICD-9-CM codes: 016.0; 095.4; 189.0; 189.9; 223.0; 236.91; 271.4; 274.1; 283.11; 403; 404; 440.1; 442.1; 572.4; 581-588; 591; 753.12-753.19; 753.2; 794.4).

** Drugs may induce diabetic retinopathy or macular edema included tamoxifen, quinine, chloroquine, hydroxychloroquine, mefloquine, digoxin, ethambutol, peginterferonalfa 2a, peginterferonalfa 2b, interferon alfa-2b, interferon alfa n3, interferon alfacon 1, interferon beta 1a, interferon alfa 1b, isocarboxazid, sildenafil, isotretinoin, vigabatrin, fingolimod, doxetaxel, niacin, and latanoprost (ophthalmic).

#Based on the measure closest to index date.

†† For clinical measures, the distribution of covariates and standardized difference were the mean of results from multiple imputation (20 iterations) as each iteration produces different number of patients with each level of clinical measure, e.g. HbA1c <7% (53mmol/mol), 7-9% (53-75mmol/mol), >9% (75mmol/mol). Availability and distribution of clinical measures were shown in Table 1.

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Supplementary Table 5. Crude and adjusted hazard ratios for advanced diabetic requiring treatment associated with use of incretin-based therapies compared with therapeutic alternatives based on multiple imputation of clinical measures (Hemoglobin A1c, blood pressure, and low-density lipoprotein cholesterol)*†‡.

Comparison	Cohort	No. of Patient	Median duration (yr) of treatment (IQR)	Person-yr	No. of Advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy requiring treatment rate per 1,000 patient-yr	Crude HR (95% CI)	PS weighting § HR (95% CI)
DPP4i vs SU	DPP4i	39,292	0.75 (0.41-1.67)	50,222	349	6.9 (6.3-7.7)	1.10 (0.97-1.25)	0.94 (0.81-1.09)
	SU	87,073	0.87 (0.42-2.01)	129,099	772	6.0 (5.6-6.4)	1.00 (reference)	1.00 (reference)
DPP4i vs TZD	DPP4i	51,410	0.80 (0.41-1.70)	67,327	520	7.7 (7.1-8.4)	0.85 (0.73-0.98)	0.92 (0.74-1.15)
	TZD	22,231	0.74 (0.41-1.52)	26,984	253	9.4 (8.3-10.6)	1.00 (reference)	1.00 (reference)
GLP1RA vs LAI	GLP1RA	9,561	0.59 (0.41-1.21)	9,462	66	7.0 (5.5-8.9)	0.49 (0.39-0.63)	0.54 (0.42-0.71)
	LAI	82,849	0.67 (0.41-1.66)	106,699	1,368	12.8 (12.2-13.5)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	10,355	0.58 (0.41-1.17)	9,895	122	10.7 (9.2-12.4)	1.16 (0.94-1.42)	0.76 (0.53-1.10)
	TZD	27,345	0.78 (0.42-1.57)	34,232	334	7.6 (6.9-8.3)	1.00 (reference)	1.00 (reference)

Abbreviations: Yr, year; ADRT, advanced diabetic retinopathy requiring treatment; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin.

*Analysis based on as treated exposure definition, latency period is 30 days.

†The distribution of covariates and standardized difference of are shown in Table S3, S4. Availability and distribution of clinical measures are shown in Table 1. ‡We conducted MI (20 iterations) using fully conditional specification with logistic regression for clinical variables (HbA1c, SBP, DBP, LDL) in arbitrary missing pattern allowing generalized logit model for nominal response data as proportional odds assumption was violated.

§Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators. The presented HR is obtained by pooling PS weighted HRs across the 20 adjusted HRs using log transformation.

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Supplementary Table 6. Crude and adjusted hazard ratios for advanced diabetic retinopathy requiring treatment associated with use of incretin-based therapies compared with therapeutic alternatives according to Hemoglobin A1c tertiles*†‡.

Stratum	Comparison	Cohort	No. of Patients	Median duration (yr) of treatment (IQR)	Person -yr	No. of Advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy rate per 1,000 person-yr	Crude HR (95% CI)	PS weighting § HR (95% CI)
HbA1c tertiles†									
<7% (53mmol/mol)	DPP4i vs SU	DPP4i	17,155	0.80 (0.41-1.77)	22,895	61	2.7 (2.1-3.4)	0.98 (0.66-1.46)	0.85 (0.55-1.32)
		SU	38,589	0.88 (0.42-2.06)	58,346	153	2.6 (2.2-3.1)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	17,024	0.81 (0.41-1.77)	22,990	112	4.9 (4.0-5.8)	0.73 (0.48-1.09)	0.85 (0.48-1.48)
		TZD	7,863	0.75 (0.41-1.56)	9,759	67	6.9 (5.4-8.7)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	3,080	0.58 (0.41-1.20)	3,088	16	5.1 (3.1-8.3)	0.51 (0.25-1.06)	0.45 (0.21-0.94)
		LAI	23,885	0.60 (0.41-1.51)	29,004	260	9.0 (7.9-10.1)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	2,741	0.59 (0.41-1.18)	2,682	19	7.0 (4.5-10.9)	0.97 (0.50-1.91)	0.77 (0.24-2.46)	
	TZD	9,316	0.80 (0.44-1.61)	12,023	77	6.4 (5.1-8.0)	1.00 (reference)	1.00 (reference)	
7-9 % (53-75 mmol/mol)	DPP4i vs SU	DPP4i	15,078	0.75 (0.41-1.66)	19,190	162	8.4 (7.2-9.8)	1.17 (0.92-1.49)	0.99 (0.75-1.30)
		SU	32,919	0.90 (0.46-2.07)	49,925	338	6.8 (6.1-7.5)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	24,629	0.81 (0.41-1.69)	32,157	266	8.3 (7.3-9.3)	0.91 (0.71-1.16)	0.99 (0.70-1.41)
		TZD	10,080	0.74 (0.41-1.52)	12,226	114	9.3 (7.8-11.2)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	4,601	0.60 (0.41-1.23)	4,599	28	6.1 (4.2-8.8)	0.54 (0.34-0.84)	0.58 (0.37-0.91)
		LAI	35,146	0.72 (0.41-1.78)	47,377	486	10.3 (9.4-11.2)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	5,029	0.59 (0.41-1.18)	4,862	59	12.2 (9.4-15.7)	1.13 (0.74-1.73)	0.75 (0.39-1.45)	
	TZD	12,890	0.79 (0.43-1.56)	16,096	161	10.0 (8.6-11.7)	1.00 (reference)	1.00 (reference)	
>9% (75 mmol/mol)	DPP4i vs SU	DPP4i	7,059	0.67 (0.41-1.48)	8,137	126	15.5 (13.0-18.5)	1.08 (0.79-1.49)	0.93 (0.65-1.32)
		SU	15,565	0.79 (0.41-1.77)	20,828	282	13.5 (12.0-15.2)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	9,758	0.76 (0.41-1.63)	12,180	143	11.7 (10.0-13.8)	0.85 (0.60-1.21)	0.88 (0.56-1.39)
		TZD	4,288	0.72 (0.41-1.46)	4,999	72	14.3 (11.3-18.0)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	1,879	0.58 (0.41-1.17)	1,776	22	12.6 (8.3-19.1)	0.55 (0.33-0.91)	0.58 (0.35-0.96)
		LAI	23,817	0.68 (0.41-1.65)	30,318	622	20.5 (19.0-22.2)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	2,585	0.58 (0.41-1.11)	2,351	44	18.7 (13.9-25.2)	1.08 (0.68-1.72)	0.77 (0.36-1.65)	
	TZD	5,138	0.74 (0.41-1.50)	6,113	96	15.8 (12.9-19.3)	1.00 (reference)	1.00 (reference)	

Abbreviations: Hemoglobin A1c , HbA1c; Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, DPP-4 inhibitor; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP, GLP-1 receptor agonist; LAI, long acting insulin;NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement.

*Analysis based on as treated exposure definition, latency period is 30 days.

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† The distribution of covariates and standardized difference of HbA1c are shown in Table S3, S4. Availability and distribution of HbA1c are shown in Table 1.

‡ We conducted MI (20 iterations) using fully conditional specification with logistic regression for clinical variables (HbA1c, SBP, DBP, LDL) in arbitrary missing pattern allowing generalized logit model for nominal response data as proportional odds assumption was violated.

§ Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators. As each iteration produces different number of patients with HbA1c <7% (53mmol/mol), 7-9% (53-75mmol/mol), >9% (75mmol/mol), we reported the mean of sample size, median duration of treatment, person-year, number of events, rate, and the pooled crude HR and pooled PS weighted HR across the 20 estimates using log transformation.

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Supplementary Table 7. Crude and adjusted hazard ratios for advanced diabetic retinopathy requiring treatment associated with use of incretin-based therapies compared with therapeutic alternatives according to presence or not of hypertension and use of angiotension-converting enzyme inhibitors or angiotension receptor blocker at cohort entry*.

Stratum	Comparison	Cohort	No. of Patients	Median duration (yr) of treatment (IQR)	Person-yr	No. of advanced diabetic retinopathy requiring treatment Events	Advanced diabetic retinopathy requiring treatment rate per 1,000 person-yr	Crude HR (95% CI)	PS weighting† HR (95% CI)
Hypertension									
No pre-existing hypertension	DPP4i vs SU	DPP4i vs SU	3,053	0.78 (0.41-1.70)	3,989	29	7.3 (5.0-10.5)	0.81 (0.54-1.22)	0.82 (0.53-1.29)
			7,901	0.85 (0.46-2.07)	11,961	102	8.5 (7.0-10.4)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i vs TZD	4,094	0.79 (0.41-1.72)	5,421	50	9.2 (7.0-12.2)	0.85 (0.55-1.33)	1.12 (0.62-2.03)
			2,272	0.78 (0.43-1.62)	2,896	32	11.0 (7.8-15.7)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA vs LAI	764	0.58 (0.41-1.16)	762	NTSR	5.3 (2.0-14.0)	0.25 (0.09-0.67)	0.34 (0.12-0.95)
			5,831	0.70 (0.41-1.72)	7,810	145	18.6 (15.7-21.9)	1.00 (reference)	1.00 (reference)
	GLP1RA vs TZD	GLP1RA vs TZD	766	0.58 (0.41-1.04)	705	NTSR	9.9 (4.7-21.0)	0.72 (0.33-1.57)	0.98 (0.40-2.38)
			2,682	0.82 (0.50-1.68)	3,537	43	12.2 (9.0-16.4)	1.00 (reference)	1.00 (reference)
With pre-existing Hypertension	DPP4i vs SU	DPP4i vs SU	36,239	0.75 (0.41-1.67)	46,233	320	6.9 (6.2-7.7)	1.14 (1.00-1.31)	0.92 (0.80-1.06)
			79,172	0.87 (0.42-2.00)	117,138	670	5.7 (5.3-6.2)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i vs TZD	47,316	0.80 (0.41-1.70)	61,906	470	7.6 (6.9-8.3)	0.85 (0.73-1.00)	0.91 (0.74-1.12)
			19,959	0.74 (0.41-1.51)	24,088	221	9.2 (8.0-10.5)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA vs LAI	8,797	0.59 (0.41-1.21)	8,701	62	7.1 (5.6-9.1)	0.53 (0.41-0.68)	0.53 (0.40-0.68)
			77,018	0.67 (0.41-1.66)	98,889	1,223	12.4 (11.7-13.1)	1.00 (reference)	1.00 (reference)
	GLP1RA vs TZD	GLP1RA vs TZD	9,589	0.58 (0.41-1.17)	9,190	115	12.5 (10.4-15.0)	1.21 (0.98-1.50)	0.75 (0.53-1.08)
			24,663	0.77 (0.41-1.56)	30,695	291	9.5 (8.4-10.6)	1.00 (reference)	1.00 (reference)
ACE inhibitors/ARB									
No baseline ACE inhibitors/ARB	DPP4i vs SU	DPP4i vs SU	10,550	0.69 (0.41-1.54)	12,746	73	5.7 (4.6-7.2)	0.90 (0.70-1.18)	0.76 (0.58-1.01)
			27,578	0.82 (0.41-1.91)	39,472	235	6.0 (5.2-6.8)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i vs TZD	12,722	0.76 (0.41-1.65)	16,190	103	6.4 (5.2-7.7)	0.72 (0.53-0.98)	0.81 (0.54-1.21)
			6,152	0.70 (0.41-1.44)	7,259	66	9.1 (7.1-11.6)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA vs LAI	2,171	0.58 (0.41-1.10)	2,024	16	7.9 (4.8-12.9)	0.51 (0.31-0.84)	0.49 (0.29-0.82)
			24,304	0.62 (0.41-1.50)	29,041	398	13.7 (12.4-15.1)	1.00 (reference)	1.00 (reference)
	GLP1RA vs TZD	GLP1RA vs TZD	2,204	0.58 (0.41-1.10)	2,040	23	11.3 (7.5-17.0)	1.08 (0.68-1.70)	0.79 (0.39-1.63)
			7,251	0.73 (0.41-1.49)	8,760	83	9.5 (7.6-11.8)	1.00 (reference)	1.00 (reference)
With baseline ACE	DPP4i vs	DPP4i	28,742	0.77 (0.41-1.73)	37,477	276	7.4 (6.5-8.3)	1.16 (1.01-1.34)	0.96 (0.82-1.12)

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inhibitors/ARB	SU	SU	59,495	0.90 (0.44-2.06)	89,627	537	6.0 (5.5-6.5)	1.00 (reference)	1.00 (reference)
	DPP4i vs	DPP4i	38,688	0.81 (0.41-1.72)	51,137	417	8.2 (7.4-9.0)	0.88 (0.74-1.05)	0.96 (0.76-1.20)
	TZD	TZD	16,079	0.75 (0.41-1.55)	19,725	187	9.5 (8.2-10.9)	1.00 (reference)	1.00 (reference)
	GLP1RA	GLP1RA	7,390	0.60 (0.41-1.24)	7,438	50	6.7 (5.1-8.9)	0.49 (0.37-0.66)	0.51 (0.38-0.68)
	vs LAI	LAI	58,545	0.70 (0.41-1.73)	77,657	970	12.5 (11.7-13.3)	1.00 (reference)	1.00 (reference)
	GLP1RA	GLP1RA	8,151	0.58 (0.41-1.18)	7,855	99	12.6 (10.3-15.4)	1.17 (0.93-1.48)	0.73 (0.49-1.07)
	vs TZD	TZD	20,094	0.81 (0.45-1.59)	25,472	251	9.9 (8.7-11.2)	1.00 (reference)	1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, DPP-4 inhibitor; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP, GLP-1 receptor agonist; LAI, long acting insulin; angiotension-converting enzyme inhibitors, ACEI; ARB, angiotension receptor blocker; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement.

*Analysis based on as treated exposure definition, latency period is 30 days.

†Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators.

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Supplementary Table 8. Crude and adjusted hazard ratios for advanced diabetic retinopathy requiring treatment associated with use of individual incretin-based therapy compared with therapeutic alternatives*†.

Stratum	Comparison	Cohort	No. of Patients	Median duration (yr) of treatment (IQR)	Person-yr	No. of Advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy requiring treatment rate per 1,000 person-yr	Crude HR (95% CI)	PS weighting† HR (95% CI)
DPP4i†									
DPP4i vs SU	Sitagliptin vs SU	Sitagliptin SU	29,613	0.76 (0.41-1.72)	39,064	266	6.8 (6.0-7.7)	1.09 (0.95-1.26)	0.91 (0.79-1.06)
			87,073	0.87 (0.42-2.01)	129,099	772	6.0 (5.6-6.4)	1.00 (reference)	1.00 (reference)
	Saxagliptin vs SU	Saxagliptin SU	5,251	0.91 (0.46-2.05)	7,411	44	5.9 (4.4-8.0)	0.95 (0.70-1.29)	0.88 (0.64-1.20)
			87,073	0.87 (0.42-2.01)	129,099	772	6.0 (5.6-6.4)	1.00 (reference)	1.00 (reference)
	Linagliptin vs SU	Linagliptin SU	4,259	0.58 (0.38-1.15)	3,614	38	10.5 (7.6-14.5)	1.40 (1.01-1.95)	0.97 (0.68-1.37)
		87,073	0.87 (0.42-2.01)	129,099	772	6.0 (5.6-6.4)	1.00 (reference)	1.00 (reference)	
	Alogliptin vs SU	Alogliptin SU	158	0.58 (0.41-1.06)	120	NTSR	NA	NA	NA
			87,073	0.87 (0.42-2.01)	129,099	772	6.0 (5.6-6.4)	1.00 (reference)	1.00 (reference)
DPP4i vs TZD	Sitagliptin vs TZD	Sitagliptin TZD	39,020	0.82 (0.41-1.75)	52,920	401	7.6 (6.9-8.4)	0.84 (0.72-0.99)	0.91 (0.75-1.10)
			22,231	0.74 (0.41-1.52)	26,984	253	9.4 (8.3-10.6)	1.00 (reference)	1.00 (reference)
	Saxagliptin vs TZD	Saxagliptin TZD	6,847	0.91 (0.50-2.01)	9,670	62	6.4 (5.0-8.2)	0.71 (0.54-0.93)	0.80 (0.58-1.10)
			22,231	0.74 (0.41-1.52)	26,984	253	9.4 (8.3-10.6)	1.00 (reference)	1.00 (reference)
	Linagliptin vs TZD	Linagliptin TZD	5,395	0.58 (0.41-1.18)	4,630	55	11.9 (9.1-15.5)	1.12 (0.83-1.50)	1.17 (0.77-1.78)
		22,231	0.74 (0.41-1.52)	26,984	253	9.4 (8.3-10.6)	1.00 (reference)	1.00 (reference)	
	Alogliptin vs TZD	Alogliptin TZD	132	0.54 (0.41-0.87)	88	NTSR	11.4 (1.6-81.5)	0.97 (0.14-6.93)	1.52 (0.21-11.21)
			22,231	0.74 (0.41-1.52)	26,984	253	9.4 (8.3-10.6)	1.00 (reference)	1.00 (reference)
GLP1RA†									
GLP1RA vs LAI	Exenatide vs LAI	Exenatide LAI	3,862	0.59 (0.41-1.21)	4,127	25	6.1 (4.1-9.0)	0.44 (0.30-0.66)	0.44 (0.30-0.65)
			82,849	0.67 (0.41-1.66)	106,699	1,368	12.8 (12.2-13.5)	1.00 (reference)	1.00 (reference)
	Liraglutide vs LAI	Liraglutide LAI	5,420	0.61 (0.41-1.25)	5,250	41	7.8 (5.7-10.6)	0.55 (0.40-0.75)	0.57 (0.41-0.78)
			82,849	0.67 (0.41-1.66)	106,699	1,368	12.8 (12.2-13.5)	1.00 (reference)	1.00 (reference)
	Albiglutide vs LAI	Albiglutide LAI	111	0.35 (0.16-0.52)	39	NTSR	NA	NA	NA
		82,849	0.67 (0.41-1.66)	106,699	1,368	12.8 (12.2-13.5)	1.00 (reference)	1.00 (reference)	
	Dulaglutide vs LAI	Dulaglutide LAI	166	0.24 (0.12-0.40)	45	NTSR	NA	NA	NA
			82,849	0.67 (0.41-1.66)	106,699	1,368	12.8 (12.2-13.5)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	Exenatide vs TZD	Exenatide TZD	3,567	0.58 (0.41-1.14)	3,700	33	8.9 (6.3-12.6)	0.87 (0.61-1.24)	0.62 (0.42-0.93)
			27,345	0.78 (0.42-1.57)	34,232	334	9.8 (8.8-10.9)	1.00 (reference)	1.00 (reference)
	Liraglutide vs TZD	Liraglutide TZD	6,395	0.61 (0.41-1.23)	6,069	88	14.5 (11.8-17.9)	1.35 (1.07-1.71)	0.84 (0.56-1.24)
		27,345	0.78 (0.42-1.57)	34,232	334	9.8 (8.8-10.9)	1.00 (reference)	1.00 (reference)	

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Albiglutide vs TZD	Albiglutide TZD	169 27,345	0.35 (0.18-0.51) 0.78 (0.42-1.57)	62 34,232	NTSR 334	16.1 (2.3-114.5) 9.8 (8.8-10.9)	1.15 (0.16-8.23) 1.00 (reference)	0.71 (0.08-6.06) 1.00 (reference)
Dulaglutide vs TZD	Dulaglutide TZD	221 27,345	0.26 (0.13-0.41) 0.78 (0.42-1.57)	63 34,232	NTSR 334	NA 9.8 (8.8-10.9)	NA 1.00 (reference)	NA 1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, DPP-4 inhibitor; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP, GLP-1 receptor agonist; LAI, long acting insulin; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement.

*Analysis based on as treated exposure definition, latency period is 30 days.

†Patients initiated two incretin-based therapies in the same class (e.g. sitagliptin and saxagliptin) on the same day were excluded. Patients were censored when switching from one incretin-based therapy to another incretin-based therapy in the same class (e.g. from sitagliptin to saxagliptin).

‡Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators.

SUPPLEMENTARY DATA

Supplementary Table 9. Crude and adjusted hazard ratios for advanced retinopathy requiring treatment associated with use of incretin-based therapies compared with therapeutic alternatives for various latency period*.

Latency period†	Comparison	Cohort	No. of Patient	Median duration (yr) of treatment (IQR)	Person-yr	No. of advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy requiring treatment rate per 1,000 patient-yr	Crude HR (95% CI)	PS weighting† HR (95% CI)
0-day latency	DPP4i vs SU	DPP4i	39,292	0.70 (0.33-1.63)	48,313	335	6.9 (6.2-7.7)	1.12 (0.98-1.27)	0.93 (0.81-1.06)
		SU	87,072	0.82 (0.39-1.97)	124,984	733	5.9 (5.5-6.3)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	51,410	0.74 (0.37-1.66)	64,937	497	7.7 (7.0-8.4)	0.87 (0.74-1.01)	0.94 (0.76-1.15)
		TZD	22,231	0.67 (0.33-1.46)	25,602	233	9.1 (8.0-10.4)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	9,561	0.53 (0.33-1.15)	8,944	65	7.3 (5.7-9.3)	0.51 (0.40-0.66)	0.52 (0.40-0.67)
		LAI	82,846	0.62 (0.33-1.63)	103,173	1,317	12.8 (12.1-13.5)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	10,355	0.53 (0.33-1.12)	9,395	115	12.2 (10.2-14.7)	1.18 (0.95-1.46)	0.83 (0.58-1.18)	
TZD	TZD	27,345	0.73 (0.40-1.50)	32,620	310	9.5 (8.5-10.6)	1.00 (reference)	1.00 (reference)	
60-day latency	DPP4i vs SU	DPP4i	39,292	0.81 (0.50-1.72)	52,076	360	6.9 (6.2-7.7)	1.07 (0.95-1.22)	0.89 (0.78-1.02)
		SU	87,073	0.92 (0.50-2.05)	133,096	811	6.1 (5.7-6.5)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	51,410	0.85 (0.50-1.75)	69,649	542	7.8 (7.1-8.5)	0.85 (0.73-0.98)	0.90 (0.74-1.09)
		TZD	22,231	0.81 (0.50-1.59)	28,344	267	9.4 (8.4-10.6)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	9,561	0.66 (0.50-1.26)	9,966	69	6.9 (5.5-8.8)	0.49 (0.38-0.62)	0.50 (0.39-0.64)
		LAI	82,849	0.73 (0.50-1.70)	110,101	1,423	12.9 (12.3-13.6)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	10,355	0.66 (0.50-1.21)	10,376	128	12.3 (10.4-14.7)	1.15 (0.94-1.41)	0.74 (0.53-1.02)	
TZD	TZD	27,345	0.84 (0.50-1.63)	35,816	351	9.8 (8.8-10.9)	1.00 (reference)	1.00 (reference)	
90-day latency	DPP4i vs SU	DPP4i	39,292	0.86 (0.58-1.77)	53,873	377	7.0 (6.3-7.7)	1.08 (0.96-1.22)	0.90 (0.79-1.03)
		SU	87,073	0.99 (0.58-2.09)	136,981	838	6.1 (5.7-6.5)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	51,410	0.91 (0.58-1.80)	71,904	553	7.7 (7.1-8.4)	0.84 (0.72-0.97)	0.88 (0.73-1.07)
		TZD	22,231	0.87 (0.58-1.65)	29,684	279	9.4 (8.4-10.6)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	9,561	0.74 (0.57-1.32)	10,457	71	6.8 (5.4-8.6)	0.48 (0.38-0.61)	0.49 (0.38-0.63)
		LAI	82,849	0.77 (0.57-1.74)	113,390	1,477	13.0 (12.4-13.7)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	10,355	0.74 (0.57-1.26)	10,840	132	12.2 (10.3-14.5)	1.14 (0.94-1.40)	0.73 (0.53-1.00)	
TZD	TZD	27,345	0.91 (0.58-1.69)	37,373	365	9.8 (8.8-10.8)	1.00 (reference)	1.00 (reference)	
180-day latency	DPP4i vs SU	DPP4i	39,292	1.03 (0.75-1.91)	58,966	419	7.1 (6.5-7.8)	1.10 (0.98-1.24)	0.91 (0.81-1.03)
		SU	87,073	1.14 (0.82-2.22)	148,018	908	6.1 (5.7-6.5)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	51,410	1.07 (0.82-1.93)	78,303	608	7.8 (7.2-8.4)	0.82 (0.72-0.94)	0.86 (0.72-1.02)
		TZD	22,231	1.07 (0.82-1.83)	33,587	321	9.6 (8.6-10.7)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	9,561	0.96 (0.69-1.48)	11,858	82	6.9 (5.6-8.6)	0.49 (0.39-0.62)	0.51 (0.41-0.64)
		LAI	82,849	0.99 (0.72-1.85)	122,650	1,605	13.1 (12.5-13.7)	1.00 (reference)	1.00 (reference)

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GLP1RA vs	GLP1RA	10,355	0.93 (0.64-1.41)	12,144	142	11.7 (9.9-13.8)	1.10 (0.91-1.34)	0.68 (0.50-0.93)
TZD	TZD	27,345	1.09 (0.82-1.86)	41,892	409	9.8 (8.9-10.8)	1.00 (reference)	1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP, DPP-4 inhibitor; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP, GLP-1 receptor agonist; LAI, long acting insulin.

*Analysis based on as treated exposure definition.

†Latency period is defined as the period allowing for retinopathy events to occur after censoring for treatment changes.

‡Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators.

SUPPLEMENTARY DATA

Supplementary Table 10. Crude and adjusted hazard ratios for advanced diabetic retinopathy associated with use of incretin-based therapies compared with therapeutic alternatives based on initial treatment analysis*.

Comparison	Cohort	No. of Patient	Median duration (yr) of treatment (IQR)	Person-yr	No. of advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy rate per 1,000 patient-yr	Crude HR (95% CI)	PS weighting† HR (95% CI)
DPP4i vs SU	DPP4i	39,292	2.24 (0.94-3.00)	76,664	532	6.9 (6.4-7.6)	1.08 (0.97-1.20)	0.89 (0.80-1.00)
	SU	87,073	2.48 (1.05-3.00)	177,577	1,131	6.4 (6.0-6.8)	1.00 (reference)	1.00 (reference)
DPP4i vs TZD	DPP4i	51,410	2.17 (0.94-3.00)	99,372	788	7.9 (7.4-8.5)	0.87 (0.77-0.97)	0.89 (0.77-1.04)
	TZD	22,231	3.00 (1.57-3.00)	51,432	454	8.8 (8.0-9.7)	1.00 (reference)	1.00 (reference)
GLP1RA vs LAI	GLP1RA	9,561	2.13 (0.89-3.00)	18,217	128	7.0 (5.9-8.4)	0.53 (0.44-0.64)	0.55 (0.45-0.66)
	LAI	82,849	1.95 (0.73-3.00)	151,157	2,006	13.3 (12.7-13.9)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	10,355	1.68 (0.66-3.00)	17,626	200	11.3 (9.9-13.0)	1.18 (1.00-1.38)	0.75 (0.58-0.98)
	TZD	27,345	3.00 (1.39-3.00)	61,317	563	9.2 (8.4-10.0)	1.00 (reference)	1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin.

*Initial treatment analysis is defined as completely ignoring treatment changes during follow-up (this mimics the intention-to-treat analysis in a randomized trial and is equivalent to an indefinite latent period). The follow-up ends with the earliest of the following events: 3 years after initiation, death, end of enrolment for Medicare Parts A, B, end of study (Sep 30, 2015), or a claim for retinopathy treatment. Patients initiated the therapy on the day of outcome occurrence, death, end of Medicare part A,B, end of study (9/30/2015) were excluded when estimating HR.

†Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators.

SUPPLEMENTARY DATA

Supplementary Table 11. Crude and adjusted hazard ratios for advanced diabetic retinopathy treatment associated with use of incretin-based therapies compared with therapeutic alternatives based on modified primary outcome*†.

Comparison	Cohort	No. of Patient	Median duration (yr) of treatment (IQR)	Person-yr	No. of advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy ate per 1,000 patient-yr	Crude HR (95% CI)	PS weighting‡ HR (95% CI)
DPP4i vs SU	DPP4i	39,292	0.75 (0.41-1.68)	50,241	330	6.6 (5.9-7.3)	1.11 (0.98-1.27)	0.92 (0.80-1.06)
	SU	87,073	0.87 (0.42-2.01)	129,173	719	5.6 (5.2-6.0)	1.00 (reference)	1.00 (reference)
DPP4i vs TZD	DPP4i	51,410	0.80 (0.41-1.70)	67,368	479	7.1 (6.5-7.8)	0.81 (0.69-0.94)	0.87 (0.71-1.06)
	TZD	22,231	0.74 (0.41-1.52)	26,992	244	9.0 (8.0-10.3)	1.00 (reference)	1.00 (reference)
GLP1RA vs LAI	GLP1RA	9,561	0.59 (0.41-1.21)	9,463	62	6.6 (5.1-8.4)	0.48 (0.37-0.62)	0.50 (0.38-0.65)
	LAI	82,849	0.67 (0.41-1.66)	106,742	1,326	12.4 (11.8-13.1)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	10,355	0.58 (0.41-1.17)	9,900	117	11.8 (9.8-14.2)	1.15 (0.93-1.42)	0.76 (0.53-1.07)
	TZD	27,345	0.78 (0.42-1.57)	34,243	322	9.4 (8.4-10.5)	1.00 (reference)	1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin.

*Analysis based on as treated exposure definition, latency period is 30 days.

† Outcome is defined as a diabetic retinopathy diagnosis in the primary, secondary, or third position within the same claim of the procedures including photocoagulation, intravitreal injection of anti-vascular endothelial growth factor agent or steroid, or vitrectomy.

‡ Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators.

SUPPLEMENTARY DATA

Supplementary Table 12. Crude and adjusted hazard ratios for advanced diabetic retinopathy requiring treatment associated with use of incretin-based therapies compared with therapeutic alternatives after restricting to patients who had an eye exam during follow-up*.

Comparison	Cohort	No. of Patient	Median duration (yr) of treatment (IQR)	Person-yr	No. of advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy requiring treatment rate per 1,000 patient-yr	Crude HR (95% CI)	PS weighting† HR (95% CI)
DPP4i vs SU	DPP4i	17,379	1.40 (0.66-2.73)	32,698	226	6.9 (6.1-7.9)	1.16 (0.99-1.36)	0.90 (0.76-1.08)
	SU	40,076	1.66 (0.79-3.14)	86,919	489	5.6 (5.1-6.1)	1.00 (reference)	1.00 (reference)
DPP4i vs TZD	DPP4i	24,174	1.37 (0.66-2.65)	44,885	349	7.8 (7.0-8.6)	0.93 (0.76-1.16)	1.09 (0.83-1.42)
	TZD	7,149	1.39 (0.67-2.58)	13,421	111	8.3 (6.9-10.0)	1.00 (reference)	1.00 (reference)
GLP1RA vs LAI	GLP1RA	3,674	1.04 (0.53-2.02)	5,408	37	6.8 (5.0-9.5)	0.51 (0.36-0.70)	0.53 (0.38-0.75)
	LAI	36,633	1.46 (0.64-2.90)	72,781	904	12.4 (11.6-13.3)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	4,433	0.94 (0.49-1.83)	5,887	75	12.7 (10.1-16.0)	1.24 (0.95-1.63)	0.87 (0.57-1.35)
	TZD	9,735	1.35 (0.67-2.54)	18,040	166	9.2 (7.9-10.7)	1.00 (reference)	1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin.

*Analysis based on as treated exposure definition, latency period is 30 days.

† Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators.

SUPPLEMENTARY DATA

Supplementary Table 13. Crude and adjusted hazard ratios for advanced diabetic retinopathy requiring treatment associated with use of incretin-based therapies compared with therapeutic alternatives after censoring patients receiving long acting insulin during follow-up*.

Comparison	Cohort	No. of Patient	Median duration (yr) of treatment (IQR)	Person-yr	No. of Advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy requiring treatment per 1,000 patient-yr	Crude HR (95% CI)	PS weighting† HR (95% CI)
DPP4i vs SU	DPP4i	39,292	0.58 (0.24-1.37)	41,610	195	4.7 (4.1-5.4)	0.94 (0.79-1.10)	0.83 (0.70-0.99)
	SU	87,073	0.69 (0.41-1.75)	113,858	532	4.7 (4.3-5.1)	1.00 (reference)	1.00 (reference)
DPP4i vs TZD	DPP4i	51,410	0.59 (0.34-1.40)	56,300	358	6.4 (5.7-7.1)	0.84 (0.70-1.00)	0.94 (0.74-1.19)
	TZD	22,231	0.58 (0.41-1.32)	23,314	181	7.8 (6.7-9.0)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	10,355	0.41 (0.11-0.73)	6,461	59	9.1 (7.1-11.8)	0.95 (0.72-1.26)	0.88 (0.58-1.31)
	TZD	27,345	0.61 (0.41-1.36)	29,566	246	8.3 (7.3-9.4)	1.00 (reference)	1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin.

*Analysis based on as treated exposure definition, latency period is 30 days.

† Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators.

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Supplementary Table 14. Crude and adjusted hazard ratios for advanced diabetic retinopathy requiring treatment associated with use of incretin-based therapies compared with therapeutic alternatives after censoring patients receiving medications that may induce or worsen diabetic retinopathy, or slow the progression of retinopathy (fenofibrate)*†.

Comparison	Cohort	No. of Patient	Median duration (yr) of treatment (IQR)	Person-yr	No. of Advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy requiring treatment rate per 1,000 patient-yr	Crude HR (95% CI)	PS weighting‡ HR (95% CI)
DPP4i vs SU	DPP4i	39,292	0.50 (0.19-1.18)	37,001	280	7.6 (6.7-8.5)	1.07 (0.92-1.23)	0.88 (0.75-1.02)
	SU	87,073	0.58 (0.23-1.42)	95,651	641	6.7 (6.2-7.2)	1.00 (reference)	1.00 (reference)
DPP4i vs TZD	DPP4i	51,410	0.58 (0.25-1.27)	51,403	433	8.4 (7.7-9.3)	0.83 (0.71-0.98)	0.91 (0.74-1.13)
	TZD	22,231	0.58 (0.31-1.19)	21,230	220	10.4 (9.1-11.8)	1.00 (reference)	1.00 (reference)
GLP1RA vs LAI	GLP1RA	9,561	0.41 (0.18-0.91)	7,203	63	8.7 (6.8-11.2)	0.55 (0.43-0.71)	0.57 (0.44-0.74)
	LAI	82,849	0.45 (0.16-1.10)	77,184	1,118	14.5 (13.7-15.4)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	10,355	0.43 (0.20-0.88)	7,609	108	14.2 (11.7-17.2)	1.23 (0.99-1.53)	0.92 (0.65-1.30)
	TZD	27,345	0.58 (0.34-1.23)	26,835	282	10.5 (9.3-11.8)	1.00 (reference)	1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin.

*Analysis based on as treated exposure definition, latency period is 30 days.

† Drugs may induce diabetic retinopathy or macular edema include tamoxifen, quinine, chloroquine, hydroxychloroquine, mefloquine, digoxin, ethambutol, peginterferonalfa 2a, peginterferonalfa 2b, interferon alfa-2b, interferon alfa n3, interferon alfacon 1, interferon beta 1a, interferon alfa 1b, isocarboxazid, sildenafil, isotretinoin, vigabatrin, fingolimod, doxetaxel, niacin, and latanoprost (ophthalmic).

‡Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators.

SUPPLEMENTARY DATA

Supplementary Table 15. Crude and adjusted hazard ratios for advanced diabetic retinopathy associated with use of IBTs compared with therapeutic alternatives based multivariate Cox regression model*.

Comparison	Cohort	No. of Patient	Median duration (yr) of treatment (IQR)	Person-yr	No. of Advanced diabetic retinopathy requiring treatment events	Advanced diabetic retinopathy rate per 1,000 patient-yr	Crude HR (95% CI)	Adjusted† HR (95% CI)
DPP4i vs SU	DPP4i	39,292	0.75 (0.41-1.67)	50,222	349	6.9 (6.3-7.7)	1.10 (0.97-1.25)	0.96 (0.84-1.10)
	SU	87,073	0.87 (0.42-2.01)	129,099	772	6.0 (5.6-6.4)	1.00 (reference)	1.00 (reference)
DPP4i vs TZD	DPP4i	51,410	0.80 (0.41-1.70)	67,327	520	7.7 (7.1-8.4)	0.85 (0.73-0.98)	0.86 (0.73-1.01)
	TZD	22,231	0.74 (0.41-1.52)	26,984	253	9.4 (8.3-10.6)	1.00 (reference)	1.00 (reference)
GLP1RA vs LAI	GLP1RA	9,561	0.59 (0.41-1.21)	9,462	66	7.0 (5.5-8.9)	0.49 (0.39-0.63)	0.51 (0.39-0.65)
	LAI	82,849	0.67 (0.41-1.66)	106,699	1,368	12.8 (12.2-13.5)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	10,355	0.58 (0.41-1.17)	9,895	122	12.3 (10.3-14.7)	1.16 (0.94-1.42)	0.94 (0.75-1.19)
	TZD	27,345	0.78 (0.42-1.57)	34,232	334	9.8 (8.8-10.9)	1.00 (reference)	1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin.

*Analysis based on as treated exposure definition, latency period is 30 days.

†Adjusted HRs from multivariate Cox regression model were based on original population without weighting.

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Supplementary Table 16. Crude and adjusted hazard ratios for incident diabetic retinopathy associated with use of incretin-based therapy compared with therapeutic alternatives based on secondary outcome*†.

Analysis†	Comparison	Cohort	No. of Patient	Median duration (yr) of treatment (IQR)	Person-yr	No. of incident diabetic retinopathy events	Incident diabetic retinopathy rate per 1,000 patient-yr	Crude HR (95% CI)	PS weighting† HR (95% CI)
0-day latency§	DPP4i vs SU	DPP4i	34,737	0.63 (0.33-1.49)	39,578	2,349	59.4 (56.9-61.9)	1.14 (1.08-1.19)	0.97 (0.92-1.02)
		SU	78,916	0.74 (0.33-1.82)	105,961	5,284	49.9 (48.5-51.3)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	45,316	0.66 (0.33-1.50)	52,753	3,331	63.1 (61.0-65.4)	0.92 (0.87-0.98)	0.95 (0.87-1.03)
		TZD	19,520	0.59 (0.33-1.32)	20,689	1,456	70.4 (66.7-74.2)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	8,536	0.50 (0.33-1.05)	7,443	501	67.3 (61.5-73.6)	0.61 (0.56-0.67)	0.62 (0.57-0.68)
		LAI	71,112	0.50 (0.33-1.36)	76,870	7,722	100.5 (98.1-102.9)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	8,973	0.50 (0.33-1.00)	7,528	681	90.5 (83.7-97.8)	1.13 (1.03-1.23)	0.87 (0.76-0.99)	
	TZD	23,898	0.63 (0.33-1.37)	26,142	1,910	73.1 (69.8-76.5)	1.00 (reference)	1.00 (reference)	
30-day latency§	DPP4i vs SU	DPP4i	34,737	0.67 (0.41-1.54)	41,183	2,501	60.7 (58.3-63.2)	1.14 (1.09-1.20)	0.97 (0.93-1.03)
		SU	78,917	0.80 (0.41-1.86)	109,486	5,564	50.8 (49.5-52.2)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	45,316	0.71 (0.41-1.55)	54,745	3,537	64.6 (62.5-66.8)	0.92 (0.87-0.98)	0.96 (0.88-1.03)
		TZD	19,520	0.66 (0.41-1.39)	21,825	1,574	72.1 (68.5-75.9)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	8,536	0.58 (0.41-1.11)	7,881	549	69.7 (63.9-75.9)	0.62 (0.57-0.68)	0.63 (0.58-0.69)
		LAI	71,115	0.58 (0.41-1.40)	79,635	8,165	102.5 (100.2-104.9)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	8,973	0.58 (0.41-1.06)	7,939	722	90.9 (84.3-98.1)	1.11 (1.02-1.21)	0.85 (0.75-0.97)	
	TZD	45,134	0.69 (0.41-1.43)	52,053	3,746	72.0 (69.6-74.4)	1.00 (reference)	1.00 (reference)	
60-day latency§	DPP4i vs SU	DPP4i	34,737	0.74 (0.50-1.58)	42,734	2,632	61.6 (59.2-64.1)	1.14 (1.09-1.20)	0.97 (0.93-1.02)
		SU	78,917	0.84 (0.50-1.90)	112,893	5,802	51.4 (50.1-52.8)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	45,316	0.75 (0.50-1.59)	56,670	3,709	65.4 (63.3-67.7)	0.91 (0.86-0.97)	0.95 (0.88-1.03)
		TZD	19,520	0.72 (0.50-1.44)	22,935	1,687	73.6 (70.0-77.3)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	8,536	0.65 (0.46-1.16)	8,304	595	71.7 (66.0-77.8)	0.63 (0.58-0.69)	0.64 (0.59-0.70)
		LAI	71,115	0.66 (0.46-1.43)	82,274	8,527	103.6 (101.3-106.0)	1.00 (reference)	1.00 (reference)
GLP1RA vs TZD	GLP1RA	8,973	0.64 (0.48-1.11)	8,330	771	92.6 (86.0-99.6)	1.12 (1.03-1.21)	0.86 (0.76-0.97)	
	TZD	23,898	0.74 (0.50-1.48)	28,741	2,174	75.6 (72.4-79.0)	1.00 (reference)	1.00 (reference)	
90-day latency§	DPP4i vs SU	DPP4i	34,737	0.79 (0.56-1.63)	44,228	2,734	61.8 (59.5-64.2)	1.14 (1.09-1.19)	0.97 (0.92-1.02)
		SU	78,917	0.90 (0.58-1.94)	116,188	6,010	51.7 (50.4-53.1)	1.00 (reference)	1.00 (reference)
	DPP4i vs TZD	DPP4i	45,316	0.82 (0.58-1.63)	58,527	3,860	66.0 (63.8-68.1)	0.91 (0.86-0.96)	0.93 (0.86-1.00)
		TZD	19,520	0.77 (0.58-1.50)	24,020	1,784	74.3 (70.8-77.9)	1.00 (reference)	1.00 (reference)
	GLP1RA vs LAI	GLP1RA	8,536	0.71 (0.50-1.22)	8,712	624	71.6 (66.1-77.6)	0.63 (0.58-0.68)	0.64 (0.59-0.70)
LAI	71,115	0.72 (0.50-1.47)	84,802	8,862	104.5 (102.2-106.8)	1.00 (reference)	1.00 (reference)		

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	GLP1RA vs TZD	GLP1RA TZD	8,973 23,898	0.68 (0.50-1.17) 0.82 (0.58-1.54)	8,704 29,996	816 2,277	93.7 (87.3-100.7) 75.9 (72.8-79.2)	1.13 (1.04-1.22) 1.00 (reference)	0.85 (0.75-0.96) 1.00 (reference)
	DPP4i vs SU	DPP4i SU	34,737 78,917	0.99 (0.66-1.76) 1.05 (0.76-2.06)	48,429 125,481	3,020 6,526	62.4 (60.1-64.7) 52.0 (50.7-53.3)	1.15 (1.10-1.20) 1.00 (reference)	0.98 (0.93-1.02) 1.00 (reference)
180-day latency§	DPP4i vs TZD	DPP4i TZD	45,316 19,520	0.99 (0.71-1.77) 0.99 (0.82-1.68)	63,743 27,149	4,257 2,011	66.8 (64.8-68.9) 74.1 (70.8-77.5)	0.92 (0.87-0.97) 1.00 (reference)	0.94 (0.88-1.01) 1.00 (reference)
	GLP1RA vs LAI	GLP1RA LAI	8,536 71,115	0.90 (0.59-1.39) 0.88 (0.51-1.58)	9,865 91,796	709 9,659	71.9 (66.7-77.5) 105.2 (103.0-107.5)	0.64 (0.59-0.69) 1.00 (reference)	0.65 (0.60-0.70) 1.00 (reference)
	GLP1RA vs TZD	GLP1RA TZD	8,973 23,898	0.84 (0.52-1.32) 0.99 (0.82-1.72)	9,739 33,598	909 2,538	93.3 (87.3-99.8) 75.5 (72.6-78.6)	1.13 (1.05-1.22) 1.00 (reference)	0.88 (0.78-0.99) 1.00 (reference)

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, Sulfonylurea; TZD, Thiazolidinedione; GLP1RA, Glucagon-like peptide-1 receptor agonist; LAI, long acting insulin.

*Analysis based on as treated exposure definition, latency period is 30 days.

†Our secondary outcome is incident diabetic retinopathy identified by diagnosis (ICD-9-CM 362.0X). Patients with baseline diabetic retinopathy were excluded in this analysis.

‡Propensity score weighted HR were standardized to the distribution of baseline covariates in incretin-based therapy initiators.

§Latency period is defined as the period allowing for retinopathy events to occur after censoring for treatment changes.